PREVALENCE OF PHARMACOLOGICAL NEUROENHANCEMENT IN SWITZERLAND AND ITS ASSOCIATIONS WITH PERSONALITY AND MENTAL HEALTH

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Success is not the key to happiness.

Happiness is the key to success.

If you love what you are doing, you will be successful.

Albert Schweitzer

ABSTRACTS

Pharmacological neuroenhancement (PNE) refers to the nonmedical use of prescription drugs and the use of alcohol or illegal drugs for the purpose of cognitive or mood enhancement at work or while studying. The doctoral thesis aimed to investigate the prevalence of PNE in Switzerland for the first time. In addition, the research aimed to identify associations with personality and mental health. The prevalence of PNE was low among the Swiss population when compared to the United States. Moreover, psychoactive substance use for mood enhancement was more common than direct cognitive enhancement. Being a student, high levels of stress, using illegal drugs and medical treatment for a mental disorder were important predictors for both forms of enhancement. The assumption that cognitive enhancement among healthy individuals will widely spread and become a desirable means to improve work and study performance was not supported by the present findings. Monitoring the development of PNE in Switzerland is essential in order to develop effective policy responses. Nevertheless, future research should transfer from first-world problems with self-optimization of already well-functioning to the preservation and recovery of health of vulnerable groups in the public.

Die Einnahme von verschreibungspflichtigen Medikamenten ohne medizinische Indikation sowie der Konsum von Alkohol und illegalen Substanzen werden als Pharmakologisches Neuroenhancement (PNE) bezeichnet, wenn damit eine kognitive Leistungssteigerung oder Stimmungsaufhellung beim Lernen oder Arbeiten bezweckt wird. Die vorliegende Doktorarbeit hatte zum Ziel, die Prävalenz von PNE in der Schweiz zu schätzen und den Zusammenhang mit Persönlichkeit und psychischer Gesundheit zu untersuchen. Verglichen mit den USA zeigte sich in der Schweiz eine niedrige Prävalenz von PNE, wobei der Substanzkonsum zur Stimmungsaufhellung am Arbeitsplatz häufiger vorkam als der Konsum zur direkten kognitiven Leistungssteigerung. Studentenstatus, hoher Stress, Erfahrung mit dem Konsum von illegalen Substanzen und aktuelle medizinische Behandlung einer psychischen Störung waren wichtige Prädiktoren für beide Formen von PNE. Die Studienergebnisse lassen nicht vermuten, dass der Konsum von psychoaktiven Substanzen zur kognitiven Leistungssteigerung stark zunehmen wird. Das Monitoring von PNE in der Schweiz ist wichtig, um im Bedarfsfall rechtzeitig zu reagieren. Dennoch sollte der Fokus nicht nur auf die Selbstoptimierung von ohnehin gut funktionierenden Personen, sondern auch auf die Erhaltung und Wiederherstellung der Gesundheit von vulnerablen Bevölkerungsgruppen gelegt werden.

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ABBREVIATIONS

12-MP	12-month prevalence
30-DP	30-day prevalence
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
BDI	Beck Depression Inventory
BIS	Barratt Impulsiveness Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
CI	Confidence Interval
DD	Delay Discounting
GCI	Global Cognitive Index
IED	Intra-Extra-Dimensional set shifting
IGT	Iowa Gambling Task
LNST	Letter Number Sequencing Task
LTP	Lifetime prevalence
M	Mean
MASC	Movie for the Assessment of Social Cognition
MET	Multifaceted Empathy Test
MPH	Methylphenidate
N / n	Sample size
OR	Odds Ratio
PAL	Paired Associates Learning
PCE	**Pharmacological cognitive enhancement**
PME	**Pharmacological mood enhancement**
PNE	**Pharmacological neuroenhancement**
RAVLT	Rey Auditory Verbal Learning Test
RVP	Rapid Visual Processing
SD	Standard deviation
SKID I/II	Structural Clinical Interview for DSM-IV Axis I/II Disorders
SNQ	Social Network Questionnaire
SR	Self-report
SWM	Spatial Working Memory
TCI	Temperament Character Inventory
U.S./ USA	The United States of America
ZuCo(2)St	Zurich Cocaine Cognition Study

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EXTENDED SUMMARY

The ever-increasing demands in education, the workplace, and social life, coupled with internal and external pressure to succeed, are assumed to require strategies to enhance cognitive function. Nonmedical use of prescription drugs and the use of illegal drugs or alcohol for the purpose of cognitive or mood enhancement to improve performance at work or while studying is referred to as pharmacological neuroenhancement. Pharmacological neuroenhancement as a functional means to improve concentration, attention, and vigilance has been increasingly focused throughout the past decade, and has been debated in scientific and bioethical literature, media, and politics. The increased stimulant production in recent years has been accompanied by a boost in published scientific literature regarding cognitive enhancement and neuroenhancement, although both increases may be explained independently. Increased stimulant production may indicate that more patients receive medical treatment for their mental disorders, which generally represents a positive development. The augmented number of publications on nonmedical stimulant use and pharmacological neuroenhancement might, on the other hand, suggest that cognitive enhancement is on the rise. However, the nonmedical use of prescription stimulants and the use of illegal drugs to enhance cognitive performance in healthy individuals are no news. New is only that the terms “cognitive enhancement” and “neuroenhancement” have been used to describe this phenomenon in the past decade. Moreover, recent studies reporting a high prevalence of pharmacological neuroenhancement showed several limitations concerning study design and representativeness of the sample, and some of them have been misinterpreted by the media.

At the beginning of this thesis, no data on pharmacological neuroenhancement in Switzerland were available. However, findings from a study on stress among Swiss employees and expert opinions indicated that psychoactive substance use for enhancement purposes might be prevalent in Switzerland. The first Swiss study on pharmacological neuroenhancement among Swiss university students revealed that every seventh student had used prescription drugs or drugs of abuse at least once in order to achieve better study performance. Consistent with studies in Europe and the United States, Ritalin®, containing the active ingredient methylphenidate, was the prescription drug most frequently misused to improve academic performance. The nonmedical use of methylphenidate and other illicit drugs for cognitive and mood enhancement by healthy individuals might cause adverse health outcomes. Therefore, the present thesis aimed, amongst others, to investigate the lifetime and

12-month prevalence of pharmacological neuroenhancement among the Swiss general population, to provide evidence-based knowledge for policy and prevention.

The first two studies of the present thesis contain findings of the first representative large-scale online survey on pharmacological neuroenhancement in Europe using a national Internet panel. This survey was designed subsequent to a feasibility study on neuroenhancement in Switzerland. More than 10,000 people participated in the epidemiological survey, and data were weighted for age, sex, and language region. In the first study concerned with these data, 4.0% of the surveyed sample reported having used prescription drugs or drugs of abuse for pharmacological neuroenhancement at least once. However, only half of them (2.1%) reported pharmacological neuroenhancement within the past year and regular use was uncommon. Pharmacological mood enhancement was more prevalent than pharmacological cognitive enhancement, and experience with one or both forms of enhancement was associated with being a student, having used illegal drugs, frequent stress, perceived poor health, and with having a mental disorder.

The second study examined the importance of stress, self-efficacy, and self-medication for pharmacological neuroenhancement based on measures referring to stress, self-efficacy, mental health, and illegal drug use in the past 12 months. Current medical treatment for a mental disorder was the strongest predictor of both pharmacological cognitive enhancement and pharmacological mood enhancement. Cannabis use, frequent stress, and long-term stress at work or in education were further predictors of both enhancement forms. Time pressure and negative stressors at work or in education were no predictors of pharmacological neuroenhancement in the overall prediction model. Pharmacological mood enhancement was positively associated with being female and negatively associated with self-efficacy. Being male, being a student, and using illegal drugs other than cannabis, were positively associated with pharmacological cognitive enhancement. The findings of this study indicate a big gap between pharmacological neuroenhancement by healthy individuals as moderate self-medication to cope with temporary stress and pharmacological neuroenhancement by individuals with a mental disorder as serious self-medication to cope with stress, symptoms, and side effects of their medical treatment.

The third study addressed cognitive, social, and personality differences between healthy individuals with regular methylphenidate use for cognitive enhancement and stimulant-naïve controls. While previous studies suggested that pharmacological cognitive enhancement aims to cope with cognitive deficits, recently abstinent cognitive enhancement users showed no cognitive deficits and even superior strategic thinking and decision-making compared to

controls. However, the neuropsychological assessment revealed that pharmacological cognitive enhancement users shared certain personality features with recreational cocaine users. For example, they displayed higher levels of self-reported impulsivity, novelty seeking, and Machiavellianism, and lower social reward dependence than controls. Moreover, they behaved more self-serving, less empathic, and less prosocial in social interaction tasks compared to controls. The highly specific personality structure of healthy individuals who engage in pharmacological cognitive enhancement and the difficulties in recruiting healthy with regular methylphenidate use for cognitive enhancement give no cause for concern that pharmacological cognitive enhancement with prescription stimulants will spread in the near future.

In conclusion, pharmacological neuroenhancement is prevalent but uncommon among the Swiss population compared to findings in the United States. Moreover, psychoactive substance use for mood enhancement is more common in Switzerland than direct cognitive enhancement. However, being a student, high levels of stress, using illegal drugs, and medical treatment for a present mental disorder were important predictors for both forms of enhancement. Pharmacological neuroenhancement as self-medication to cope with symptoms of a mental disorder and associated stress was identified as an important public health issue that has up-to-date achieved minor attention. The assumption that cognitive enhancement among healthy individuals will widely spread and become a desirable means to improve work and study performance was not supported by the present findings. Monitoring the development of pharmacological neuroenhancement in Switzerland is essential in order to develop effective policy responses. Nevertheless, future research should transfer from first-world problems with self-optimization of already good functioning to the preservation and recovery of health of vulnerable groups in the public. Moreover, while regular prescription drug misuse for cognitive and mood enhancement in Switzerland is rare, regular use of alcohol and cannabis to relieve stress is more common and affects physical and mental health. Future research on pharmacological neuroenhancement considering the complexity of psychoactive substance use for improved performance at work and in education is therefore recommended. Building on the present findings, future studies should not be limited to healthy individuals and use longitudinal designs.

AUSFÜHRLICHE ZUSAMMENFASSUNG

Strategien zur kognitiven Leistungssteigerung erscheinen notwendig, um den ständig wachsenden Anforderungen in der Ausbildung, am Arbeitsplatz sowie auch in sozialen Bereichen des Lebens gerecht zu werden und dem Erfolgsdruck standzuhalten. Der nicht medizinisch indizierte Gebrauch von verschreibungspflichtigen Medikamenten und der Gebrauch von illegalen Drogen und Alkohol zur Leistungssteigerung am Arbeitsplatz oder in der Ausbildung werden als Pharmakologisches Neuroenhancement bezeichnet. Im vergangenen Jahrzehnt wurde sowohl in der wissenschaftlichen und bioethischen Literatur als auch in Medien und Politik vermehrt über pharmakologisches Neuroenhancement als Instrument zur Verbesserung der Konzentration und Aufmerksamkeit und Reduktion von Müdigkeit debattiert. Das Produktionswachstum von verschreibungspflichtigen Stimulanzien ging einher mit einem Anstieg an Publikationen zum Thema "Cognitive Enhancement" und "Neuroenhancement". Die beiden Anstiege müssen jedoch prinzipiell unabhängig voneinander erklärt werden. Die Zunahme der Produktion von verschreibungspflichtigen Medikamenten weist darauf hin, dass immer mehr Personen mit einer psychischen Störung medizinisch behandelt werden, was grundsätzlich eine positive Entwicklung widerspiegeln kann. Beim Zuwachs an Publikationen zum nicht medizinischen Gebrauch von Medikamenten oder pharmakologischem Neuroenhancement stellt sich hingegen die Frage, ob auch der Substanzgebrauch zur kognitiven Leistungssteigerung stetig zunimmt. Dass gesunde Personen ohne medizinische Notwendigkeit verschreibungspflichtige Stimulanzien und illegale Drogen konsumieren, um damit ihre kognitive Leistungsfähigkeit zu verbessern, ist dabei nichts Neues. Neu ist lediglich, dass dafür die Begriffe "Cognitive Enhancement" und "Neuroenhancement" verwendet werden. Studien, die eine hohe Prävalenz von pharmakologischem Neuroenhancement berichteten, wiesen partiell Mängel im Studiendesign oder Repräsentativität der Stichprobe auf und wurden von den Medien teilweise falsch interpretiert.

Zu Beginn dieser Dissertation lagen noch keine Daten zum pharmakologischen Neuroenhancement in der Schweiz vor. Ergebnisse einer Stressstudie bei Schweizer Angestellten und Expertenmeinungen wiesen jedoch darauf hin, dass der Gebrauch von psychoaktiven Substanzen zur Leistungsverbesserung auch in der Schweiz stattfindet. Die erste Studie bei Schweizer Studierenden kam zum Schluss, dass bereits jede/r siebte Studierende verschreibungspflichtige Medikamente oder andere psychoaktive Substanzen eingesetzt hatte, um damit die Gehirnleistung im Studium zu verbessern. Konsistent mit

Studien aus Europa und den USA, wurde auch in der Schweiz Ritalin®, ein Medikament mit dem Wirkstoff Methylphenidat, am häufigsten zur Verbesserung der Studienleistung eingesetzt. Der nicht medizinisch indizierte Gebrauch von Methylphenidat und anderen psychoaktiven Substanzen zur kognitiven Leistungssteigerung oder Stimmungsaufhellung kann negative Konsequenzen für die Gesundheit von gesunden Personen haben. Daher war eines der Ziele der vorliegenden Dissertation, die Lebenszeit- und 12-Monats-Prävalenz von pharmakologischem Neuroenhancement in der Schweiz zu bestimmen, um evidenzbasiertes Wissen für Politik und Prävention zu generieren.

Die ersten beiden Studien dieser Dissertation beziehen sich auf die erste umfassende, repräsentative Online-Umfrage zum Thema pharmakologisches Neuroenhancement in Europa. Die Daten wurden mithilfe eines nationalen Internet-Panels erhoben. Die Umfrage wurde in Anlehnung an eine zuvor durchgeführte Machbarkeitsstudie zu Neuroenhancement in der Schweiz konzipiert. Insgesamt haben mehr als 10,000 Personen an der Online-Umfrage teilgenommen und die Daten wurden nach den Bevölkerungsmerkmalen Alter, Geschlecht und Sprachregion gewichtet. Die erste Studie bezieht sich auf die Prävalenz und zeigt auf, dass 4.0% der Umfrageteilnehmenden bereits einmal verschreibungspflichtige Medikamente oder Drogen zur kognitiven Leistungssteigerung oder Stimmungsaufhellung am Arbeitsplatz oder in der Ausbildung eingesetzt haben. Nur die Hälfte davon (2.1%) berichtete auch von pharmakologischem Neuroenhancement im vergangenen Jahr und der regelmässige Gebrauch war selten. Der Gebrauch von psychoaktiven Substanzen zur Stimmungsaufhellung wurde häufiger berichtet als der Gebrauch zur direkten kognitiven Leistungssteigerung, und beide Formen wurden mit Ausbildungsstatus, illegalem Drogenkonsum, häufigem Stress, subjektiv schlecht eingeschätzter Gesundheit und der Diagnose einer psychischen Störung in Verbindung gebracht.

In der zweiten Teilstudie dieser Arbeit wurde anhand der Daten zu Stress, Selbstwirksamkeitserwartung, psychischer Gesundheit und illegalem Drogenkonsum in den letzten 12 Monaten die Relevanz von Stress, Selbstwirksamkeit und Selbstmedikation für pharmakologisches Neuroenhancement untersucht. Die aktuelle medizinische Behandlung einer psychischen Störung war der beste Prädiktor für den Gebrauch von psychoaktiven Substanzen sowohl zur kognitiven Leistungssteigerung als auch zur Stimmungsaufhellung. Cannabiskonsum und häufiger Stress sowie Langzeitstress am Arbeitsplatz oder in der Ausbildung waren weitere Prädiktoren für beide Formen von pharmakologischem Neuroenhancement. Zeitdruck und negative Stressoren am Arbeitsplatz oder in der Ausbildung trugen nicht zur Vorhersage im Gesamtmodell bei. Der Gebrauch von

psychoaktiven Substanzen zur Stimmungsaufhellung stand in positivem Zusammenhang mit weiblichem Geschlecht und in negativem mit der Selbstwirksamkeitserwartung. Der Gebrauch von psychoaktiven Substanzen zur kognitiven Leistungssteigerung wurde positiv assoziiert mit männlichem Geschlecht, Ausbildungsstatus und dem Gebrauch von weiteren illegalen Drogen nebst Cannabis. Die Ergebnisse dieser Studie deuten darauf hin, dass grosse Unterschiede existieren zwischen gesunden Personen, die pharmakologisches Neuroenhancement als moderate Selbstmedikation zur temporären Stressbewältigung einsetzen und Personen mit psychischen Störungen, die pharmakologisches Neuroenhancement als intensive Selbstmedikation zur Bewältigung von Stress, Symptomen und Medikamentennebenwirkungen einsetzen.

Die dritte Studie der vorliegenden Dissertation hatte zum Ziel, Unterschiede in Kognition, sozialem Verhalten und Persönlichkeit zu finden zwischen Personen, die regelmässig ohne Indikation Methylphenidat zur kognitiven Leistungssteigerung einsetzen und gesunden Personen als Kontrollgruppe ohne Stimulanziengebrauch. Während frühere Studien den Gebrauch von psychoaktiven Substanzen zur kognitiven Leistungssteigerung als mit vorhandenen kognitiven Defiziten assoziiert berichtet haben, zeigten Personen, die regelmässig Methylphenidat zur kognitiven Leistungssteigerung einsetzen, während der Testung jedoch abstinent waren, keine kognitiven Defizite und waren der Kontrollgruppe im strategischen Denken und bei der Entscheidungsfindung sogar überlegen. Die neuropsychologische Untersuchung konnte zudem zeigen, dass Personen, die Substanzen zur kognitiven Leistungssteigerung einsetzten, ein ähnliches Persönlichkeitsprofil aufwiesen wie Personen, die gelegentlich Kokain konsumieren. Sie zeigten höhere Werte für Impulsivität, Novelty Seeking, Machiavellismus und tiefere Werte für Social Reward Dependence als die Kontrollgruppe. Ausserdem verhielten sie sich häufiger eigennützig, weniger empathisch und weniger prosozial in sozialen Interaktionen, verglichen mit der Kontrollgruppe. Die hoch spezifische Persönlichkeitsstruktur von gesunden Personen, die Methylphenidat zur kognitiven Leistungssteigerung einsetzen, und die Schwierigkeit, gesunde Personen zu finden, die regelmässig Methylphenidat zur kognitiven Leistungssteigerung einsetzen, geben wenig Anlass zur Sorge, dass sich der Gebrauch von verschreibungspflichtigen Stimulanzien zur kognitiven Leistungssteigerung in naher Zukunft stark verbreiten würde.

In der Synopse aller Befunde kommt pharmakologisches Neuroenhancement in der Schweiz zwar vor, liegt aber weit hinter den Konsumgewohnheiten in den USA zurück. In der Schweiz ist der Gebrauch von psychoaktiven Substanzen zur Stimmungsaufhellung weiter verbreitet als der Gebrauch zur direkten kognitiven Leistungssteigerung. Ausbildungsstatus,

häufiger Stress, der Konsum von illegalen Drogen und die medizinische Behandlung einer psychischen Störung sind wichtige Prädiktoren für beide Formen von Neuroenhancement. Pharmakologisches Neuroenhancement als Selbstmedikation zur Reduktion von Symptomen einer psychischen Störung und damit verbundenem Stress wurde als wichtige Angelegenheit des öffentlichen Gesundheitswesens identifiziert, die bis heute nur wenig Aufmerksamkeit erhalten hat. Die Vermutung, dass gesunde Personen immer häufiger psychoaktive Substanzen zur kognitiven Leistungssteigerung einsetzen werden und dies somit eine gefragte Strategie zur Verbesserung der Arbeits- oder Studienleistung wird, konnte anhand der vorliegenden Ergebnisse bislang nicht bestätigt werden. Die Beobachtung der Entwicklung von pharmakologischem Neuroenhancement in der Schweiz ist jedoch unerlässlich, um auch auf politischer Ebene effektive Strategien im Anlassfall bereitstellen zu können. Allerdings sollte sich zukünftige Forschung wieder weg von der Selbstoptimierung von ohnehin gut funktionierenden Personen und hin zur Erhaltung und Wiederherstellung der Gesundheit in vulnerablen Gruppen der Bevölkerung bewegen. Während der regelmässige Gebrauch von psychoaktiven Substanzen zur kognitiven Leistungssteigerung in der Schweiz eher eine Seltenheit darstellt, ist der Gebrauch von Alkohol und Cannabis zur Stressbewältigung verbreitet und wirkt sich negativ auf die Gesundheit der Bevölkerung aus. Zukünftige Forschung zu pharmakologischem Neuroenhancement sollte die Komplexität des Gebrauchs von psychoaktiven Substanzen zur Verbesserung der Arbeits- oder Studienleistung adäquat berücksichtigen. Basierend auf den vorliegenden Ergebnissen wird empfohlen, Längsschnittstudien zu pharmakologischem Neuroenhancement zu planen, die sich nicht nur auf den Substanzgebrauch von gesunden Personen beschränken.

1 General introduction

1.1 Thesis outline

The present thesis addresses the issue of pharmacological neuroenhancement in Switzerland, and is structured in five main chapters. The first chapter provides a theoretical background of pharmacological neuroenhancement and reviews recent epidemiological findings on pharmacological neuroenhancement in the United States, Europe, and Switzerland. A clear definition of pharmacological neuroenhancement is presented, and several theoretical models about motives for pharmacological neuroenhancement are outlined and discussed. Relevant literature concerning the efficacy and consequences of pharmacological neuroenhancement is summarized, and important ethical and legal considerations are investigated. Finally, the first chapter presents an overview of the original research conducted in the present thesis and an outline of aims and hypotheses of all three studies. Chapter 2 contains the first study which addressed the prevalence of and motives for pharmacological neuroenhancement among Swiss employees and students. In the second study, delineated in Chapter 3, associations of stress and self-efficacy with pharmacological neuroenhancement, and the application of two self-medication models for pharmacological neuroenhancement are investigated. The third study, presented in Chapter 4, examines cognitive, social, and personality characteristics of healthy individuals with regular methylphenidate use for cognitive enhancement compared to stimulant-naïve controls. In the final chapter, the findings of the three studies are summarized, strengths and limitations are discussed, and implications for policy, prevention, and future research are suggested.

1.2 The neuroenhancement debate

There seems to be gradual awareness that many people are interested in enhancing themselves. They would like to be smarter, more self-confident, better looking, and thoroughly happy (Miller & Wilsdon, 2006). The growth in the market for so called human enhancement agents, such as drugs with beneficial effects on cognition, has been driven by a perfect bond of manufacturers (pharmaceutical companies), distributors (doctors and pharmacists), and a new generation obsessed with vanity and the defiance of age (Abraham, 2010; Miller & Wilsdon, 2006). Therefore, it is assumed that college students, office executives, and scientists use pharmaceuticals as little helpers to achieve the best grade, bonus or more publications and that this use will increase in the near future (Greely et al., 2008; Sahakian & Morein-Zamir, 2007). The nonmedical use of prescription drugs, alcohol or illegal drugs of abuse for the purpose of cognitive or mood enhancement at work or while

studying is referred to as pharmacological neuroenhancement (Maier & Schaub, 2015). The terms cognitive enhancement and brain doping are used when the use aims to improve cognitive function immediately for learning or other tasks with high cognitive demands.

Nonmedical prescription drug misuse for academic performance enhancement was more prevalent among U.S. college students (McCabe, West, Teter, & Boyd, 2014; Weyandt et al., 2009) than in Europe (Franke, Bonertz, et al., 2011; Maier & Schaub, 2015). However, regular use of pharmacological neuroenhancement is neither common in the United States nor in Europe, and the use of such drugs as study aid is usually limited to specific time periods, such as exam preparation (Hildt, Lieb, & Franke, 2014; Maier, Liechti, Herzig, & Schaub, 2013). Nevertheless, irregular and low-dose usage of drugs for neuroenhancement is associated with adverse reactions and the risks of long-term use are unknown (Racine & Forlini, 2008). The potential negative consequences are often trivialized by users, especially with medications approved and accepted to treat mental disorders in children (Forlini & Racine, 2009). This may falsely imply that the use is safe in healthy adult individuals as well. So far, no drug has been proven to be safe and effective when regularly used for cognitive enhancement in healthy individuals (Schleim & Quednow, 2015).

A recent increase in media coverage of innovations in neuroscience has contributed to the awareness of beneficial drug effects in patients (Farah et al., 2004; Partridge, Bell, Lucke, Yeates, & Hall, 2011). Moreover, the twenty-first century was titled “the century of neuroscience”, predicting that humans will improve their ability to modify their own brain (Farah et al., 2004). Prescription drugs developed to treat symptoms of mental disorders, such as deficits in memory, learning, attention, and motivation, became the main focus of enhancement in healthy individuals.

However, the nonmedical use of prescription drugs to improve cognitive function in healthy individuals beyond what is necessary to sustain or restore health (Juengst, 1998) is nothing new and was already prevalent among college students more than ten years ago (Farah et al., 2004; Schleim & Quednow, 2015; Wood, Sage, Shuman, & Anagnostaras, 2014). Methylphenidate (e.g., Ritalin®, Concerta®, Medikinet®) and amphetamines (e.g., Adderall®), used for the treatment of attention-deficit hyperactivity disorder (ADHD), and modafinil (e.g., Modasomil®, Provigil®), used for the treatment of narcolepsy, are the prescription drugs most frequently discussed as potential cognitive enhancers in healthy individuals (Farah, Smith, Ilieva, & Hamilton, 2014; Repantis, Schlattmann, Laisney, & Heuser, 2010). Further medications either developed to treat cognitive impairment associated with dementia or developed based on theoretical understanding of complex cognitive

processes underlying learning and memory were characterized as potential cognitive enhancers among healthy individuals as well (Repantis, Laisney, & Heuser, 2010; Wade, Forlini, & Racine, 2014). Although additional medication altering the central nervous system in a desirable way were promised, high development costs of new drugs and difficulties with their clinical approval processes have caused the abandonment of research and production in some companies (Schleim & Quednow, 2015).

The public debate on neuroenhancement begun when Sahakian and Morein-Zamir (2007) claimed that nonmedical prescription drug use was increasingly reported by shift-work employees, such as surgeons and nurses, military personal and academic professionals. The authors' understanding of function of cognitive enhancement drug use was to study longer, work more efficiently, or to simply cope with stress. At the same time, they wondered how many of their scientific colleagues use cognitive enhancement drugs. In a non-representative online poll among readers of the scientific journal *Nature*, every fifth among 1400 respondents indicated to have already used prescription drugs, such as methylphenidate, modafinil, or beta-blockers to improve cognitive function or to reduce anxiety (Maher, 2008).

While early scientific investigations preferred terms with negative notations, such as prescription drug abuse and misuse, bioethical literature rather described the desired effect as cognitive or performance enhancement (Racine & Forlini, 2008). The trend to use the term "enhancement" when referring to psychoactive substance use aiming to improve working or studying performance has even strengthened recently. Although enhanced neurotransmission is not necessarily related to actual performance enhancement (Nyberg, 2014; Repantis, 2013). The efficacy of the so called pharmacological "enhancers" can vary as a function of mechanism, dose, baseline performance, baseline dopamine levels, task, and further inter- and intra-individual differences in responding to the substance (Clatworthy et al., 2009; Husain & Mehta, 2011; van der Schaaf, Fallon, Ter Huurne, Buitelaar, & Cools, 2013). Consequently, cognitive or at least motivational enhancement by using psychoactive substances in healthy individuals is possible under certain conditions, but side effects, missing effects, and even contrary effects are also likely to occur (Repantis, 2013; Wood et al., 2014). Therefore, Repantis et al. (2010) claimed that the high expectations regarding the effectiveness of these drugs exceed their actual effects. This was confirmed in a study on pharmacological neuroenhancement among Swiss students in which only a small majority reported that their expectations were fulfilled while approximately half of them considered the repeated use to improve academic performance (Maier et al., 2013).

This is also the reason why the often made comparison between brain doping and doping in sports is not appropriate, although it may seem self-evident. While doping in sports is effective in improving physical performance, the effect of drugs used for pharmacological enhancement is more complex and difficult to predict. Nevertheless, it is claimed that both forms of doping share a competitive intention and both users assume that their competitors dope as well (Cakic, 2009; Lucke, Bell, Partridge, & Hall, 2011a). However, pharmacological neuroenhancement is not solely based on competitive motives and curiosity is an important motive for experimental use (Singh, Bard, & Jackson, 2014).

1.3 Epidemiology of pharmacological neuroenhancement

1.3.1 Difficulties in interpreting study findings

Despite a large number of recent studies on pharmacological neuroenhancement, the majority of the conducted studies show a lack of representativeness of samples and specify mainly students' use (Maier & Schaub, 2015). Furthermore, the comparison of studies is difficult due to significant differences in the definition of the construct, the inclusion criteria chosen, and the substances included in the studies (Barrett, Meisner, & Stewart, 2008; Maier & Schaub, 2015). Moreover, recent research has mainly focused on the prevalence of pharmacological cognitive enhancement (PCE), however rarely addressed pharmacological mood enhancement (PME). These issues will be addressed in the following chapter, after an overview of existent studies on the prevalence of neuroenhancement.

1.3.2 Prevalence in the United States

The nonmedical use of prescription drugs at U.S. colleges has been the origin of the recent neuroenhancement debate and has influenced subsequent studies in Europe remarkably (McCabe, 2008; McCabe, Knight, Teter, & Wechsler, 2005; Novak, Kroutil, Williams, & Van Brunt, 2007). The nonmedical use of prescription stimulants, primarily ADHD medications, has been reported to be highly prevalent among U.S. college students (Arria et al., 2008; Chen et al., 2014; Hartung et al., 2013; Rabiner, Anastopoulos, Costello, Hoyle, & Swartzwelder, 2010). In 2001, 6.9% of a representative student sample across 199 U.S. universities (*N*.=.10,904) reported the nonmedical use of prescription stimulants. A survey at a public university (*N*.=.1,811) revealed that even 34% of the respondents reported the nonmedical use of ADHD stimulants in periods of high academic stress (DeSantis, Webb, & Noar, 2008). The National Survey on Drug Use and Health (NSDUH), the Monitoring the Future (MTF), and the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) are the

three largest national surveys on nonmedical prescription drug use. They indicated that especially young adults from 18 to 25 years of age showed high prevalence rates of prescription drug misuse (Kroutil et al., 2006; McCabe, Boyd, & Teter, 2009). In a review of 21 studies (*N*.=.113,145), Wilens et al. (2008) found a past-year prevalence of nonmedical prescription stimulant use among college students of 5% to 35%, however without specifying the purpose of the nonmedical use. Nonetheless, even these large U.S. national studies had failed to identify the motives for nonmedical prescription stimulant use (Boyd & McCabe, 2008). In the same year, Racine and Forlini (2008) specified that nonmedical stimulant use for academic performance enhancement among college students ranged from 3% to 11%. This was in line with a previous review on the misuse of study drugs which suggested a lifetime prevalence of 7% and a past-year prevalence of 4% (Sussman, Pentz, Spruijt-Metz, & Miller, 2006). However, a recent study confirmed the increasing trend of nonmedical prescription stimulant use among U.S. college students which parallels an increase in medical use (McCabe et al., 2014). Again, the purpose of use was not specified.

1.3.3 Prevalence in Europe

The prevalence of pharmacological neuroenhancement in Europe is reported to be lower than in the United States (Maier & Schaub, 2015). Nevertheless, pharmacological neuroenhancement is prevalent among European students and lifetime and 12-month prevalence range from 1% to 20% (Dietz et al., 2013; Franke et al., 2013; Mache, Eickenhorst, Vitzthum, Klapp, & Groneberg, 2012; Middendorff, Poskowsky, & Isserstedt, 2012). One of the first studies on pharmacological neuroenhancement use among German students (*N*.=.512) revealed that 0.8% used prescription stimulants, such as methylphenidate and amphetamines, and that 2.9% used illegal stimulants such as amphetamine, cocaine, and ecstasy to achieve better academic performance (Franke, Bonertz, et al., 2011). In fact, this was one of the few studies which found that the use of illegal stimulant drugs for cognitive enhancement was more prevalent than the use of prescription drugs for cognitive enhancement.

Further studies among German students revealed a prevalence of pharmacological neuroenhancement of 2% (Mache et al., 2012) and 7% (Eickenhorst, Vitzthum, Klapp, Groneberg, & Mache, 2012). The German study with the largest student sample (*N*.=.8,000) revealed that 84% of the students were informed about students' substance use for academic performance enhancement, but only 5% reported having used prescription drugs or illegal drugs of abuse for pharmacological neuroenhancement (Middendorff et al., 2012). This study indicated that various prescription drugs (1.3%), cannabis (1.2%), and methylphenidate

(1.0%) were the substances most commonly used to improve study performance. A recent study using the randomized response technique found a past-year prevalence of neuroenhancement of 20% among German students (Dietz et al., 2013). However, this rate appears to be overestimated considering that caffeinated tablets were included in the definition of neuroenhancement.

Studies in other European countries found similar rates for neuroenhancement among college students. In a recent study among UK students (*N.*=.877), less than 10% reported the lifetime use of methylphenidate, modafinil, or amphetamines for cognitive enhancement and less than 4% reported current pharmacological neuroenhancement (Singh et al., 2014). A study among Flemish students (*N.*=.18,000) reported a lifetime prevalence of stimulant use of 6.9% and a past-year prevalence of 4.3% (Van Hal, Rosiers, Ponnet, & Wouters, 2013). Nonmedical use was higher during exam periods (Van Hal et al., 2013). A study among Italian undergraduate students (*N.*=.77) revealed a lifetime prevalence of substance use for cognitive enhancement of 16.0%, but the medication was primarily bought at pharmacies and it remained unclear whether the students misused prescription drugs or bought over-the-counter drugs for enhancement purposes (Castaldi et al., 2012).

Only one German study (*N.*=.3,000) addressed pharmacological neuroenhancement among employees, at the age of 20 to 50 years old. The study revealed that 17% reported using prescription drugs for cognitive or mood enhancement at work, but only 5% reported nonmedical use of prescription drugs for neuroenhancement (Kordt, 2009). These findings illustrate another aspect of the difficulty to classify and define neuroenhancement. However, the regular nonmedical use of prescription drugs for enhancement purpose was only reported by 1-2% of respondents (Kordt, 2009).

1.3.4 Prevalence in Switzerland

At the beginning of this thesis, the prevalence of pharmacological neuroenhancement in Switzerland was largely unknown (Bruggisser, Bodmer, & Liechti, 2012). Only one non-representative survey among Swiss employees (*N.*=.1,006) indicated that stress has been increasing and that 4% of the respondents reported past-year use of substances to improve their cognitive performance or their mood at work (Grebner, Berlowitz, Alvarado, & Cassina, 2010). This single study and few unpublished student theses, however, were the only evidence for pharmacological neuroenhancement in Switzerland. Nonetheless, methylphenidate prescriptions increased between 2006 and 2009 (Kühne & Rapold, 2011).

We conducted the first Swiss study on pharmacological neuroenhancement among students of three Swiss universities (*N.*=.6,275) which revealed that 13.8% had already used

prescription drugs, alcohol or illegal drugs to improve cognitive function while studying (Maier et al., 2013). Methylphenidate (4.1%), sedatives (2.7%), and beta-blockers (1.2%) were the prescription drugs most likely used for enhancement reasons. Surprisingly, 5.6% of the students reported having used alcohol to help study and 2.5% reported having used cannabis for neuroenhancement, whereas the use of illegal stimulants such as amphetamine and cocaine was mainly reported for recreational reasons and not to help studying. Pharmacological neuroenhancement was mainly reported during exam preparation but not during exams, and daily use of neuroenhancement was uncommon. Products containing caffeine, on the other hand, were used for enhancement purposes on a daily basis. However, the main motives for neuroenhancement were increased cognitive performance to support learning and increased relaxation to improve sleep to study better the following day. In line with previous research, friends were the main source of supply for prescription and illegal drugs used for neuroenhancement purposes (Bavarian, Flay, Ketcham, & Smit, 2013; Maier et al., 2013). Students justified pharmacological neuroenhancement when indicated and medically advised for the treatment of mental health or sleeping disorders and only 15.5% reported seeing no justifiable reason for neuroenhancement at all.

A second study that focused on Swiss university students (*N.*=.1,765) found that 6.2% had used methylphenidate, modafinil, or amphetamines for cognitive enhancement at least once (Ott & Biller-Andorno, 2014). The cognitive enhancement users were mostly male, showed little or no interest in religion, and reported illegal drug use more frequently (Ott & Biller-Andorno, 2014). In addition, a recent study on young Swiss men (*N.*=.5,967) found that 3% reported using neuroenhancement drugs without specifying the reason for use (Deline et al., 2014). Nevertheless, the authors assumed that more frequent use among non-college males aimed to get high while sporadic use among students might indicate cognitive enhancement to improve academic success (Deline et al., 2014).

Swiss psychiatrists and general practitioners reported only few requests for non-indicated drugs for neuroenhancement purposes (Ott, Lenk, Miller, Neuhaus Bühler, & Biller-Andorno, 2012). These low request rates are likely to be explained by the fact that students receive prescription drugs for neuroenhancement most commonly from friends (Maier et al., 2013; Ott & Biller-Andorno, 2014). In their study, Ott et al. (2012) included four clinical case scenarios of requests for pharmacological neuroenhancement and investigated how Swiss practitioners would decide on neuroenhancement requests. Most respondents would not prescribe medication without having diagnosed a clear indication but two thirds approved exceptions depending on individual's suffering. More than half of them were willing to

prescribe drugs to a student who is in urgent need for passing his final exams if no therapeutic alternative was available. Beta-blockers were the drugs most indicated. Practitioners' willingness to prescribe drugs for a scientist's jetlag was considerably low and modafinil would have been the drug most likely prescribed. However, if the case scenario referred to a young woman reporting low self-esteem or a single mother with two kids, who is overwhelmed by caring for her terminally ill mother, the practitioners were noticeably more likely to prescribe a drug, most commonly antidepressants. In summary, Swiss practitioners showed considerable openness concerning neuroenhancement without even being familiar with the term neuroenhancement (Ott et al., 2012). Given that physician's subjective norms and attitudes have a strong influence on their prescribing behavior (Ponnet, Wouters, Van Hal, Heirman, & Walrave, 2014), the dialogue about evidence-based findings of health risks and side effects of neuroenhancement drugs is strongly recommended.

1.4 Definition of pharmacological neuroenhancement

Pharmacological neuroenhancement refers to the misuse of prescription drugs, alcohol, and illegal drugs for the purpose of enhancing cognition, mood, or pro-social behavior to ultimately perform better at work or to improve study performance (de Jongh, Bolt, Schermer, & Olivier, 2008; Franke & Lieb, 2010; Maier & Schaub, 2015). In our overview article on pharmacological neuroenhancement in Europe, we provided a non-exhaustive list of psychoactive substances used as potential neuroenhancers (see Figure 1). The prescription drug most frequently misused for neuroenhancement purposes is methylphenidate (Maier & Schaub, 2015; McCabe et al., 2014; Outram, 2010). Modafinil and amphetamine salts are also frequently discussed in the context of neuroenhancement. The use of antidepressants for pharmacological mood enhancement was found to be prevalent among German surgeons (Franke et al., 2013) although studies revealed no effects among healthy individuals (Repantis, Schlattmann, Laisney, & Heuser, 2009). However, the efficacy of a drug is of secondary importance for the definition of neuroenhancement while its expected efficacy and the intention of improving cognition or mood is

Most studies have solely addressed the misuse of prescription and other illicit stimulants for cognitive enhancement (Arria et al., 2008; Franke, Bonertz, et al., 2011; Ott & Biller-Andorno, 2014; Wilens et al., 2008) and did not examine the use of other psychoactive substances with rather sedative but potentially cognitive or mood enhancing effects. Notwithstanding, the misuse of prescription drugs happens for many of the same reasons as alcohol and illegal drugs and both are problematic if they become a normalized feature of

everyday life (Silva, Kecojevic, & Lankenau, 2013). Few European studies considered alcohol, cannabis, and tranquilizers as means of cognitive enhancement (e.g., increased concentration at low doses) and enhanced psychological well-being (e.g., relaxation, stress relieve; Mache et al., 2012; Maier et al., 2013; Middendorff et al., 2012). The motives for the use of psychoactive substances indicate whether the use is referred to as neuroenhancement or not. Maier and Schaub (2015) argued that even a post-work beer to cope with stress experienced at work or in education might be considered as neuroenhancement if not used recreationally. Including such examples would lead to a substantial increase of prevalence of pharmacological neuroenhancement.

Furthermore, over-the-counter drugs and freely available products with enhancing effects, such as caffeinated products, vitamins, and food supplements are called smart drugs as well (Singh et al., 2014). Thus, they are sometimes included under a broad definition of the term *pharmacological* neuroenhancement (Franke & Lieb, 2010). However, they are excluded by the narrow definition and instead referred to as *soft enhancement* (Maier et al., 2013; Maier & Schaub, 2015; Middendorff et al., 2012). The use of those substances as functional means to improve performance at work or while studying is a key aspect of both enhancement types (Wolff & Brand, 2013). Yet, serious adverse reactions result rather of the misuse of prescription drugs, illegal drugs, or high quantities of alcohol than soft enhancement. The inclusion of soft-enhancers would again cause an augmentation of the prevalence of pharmacological neuroenhancement. Therefore, a well-reasoned and clear definition of neuroenhancement is strongly recommended for studies on pharmacological neuroenhancement.

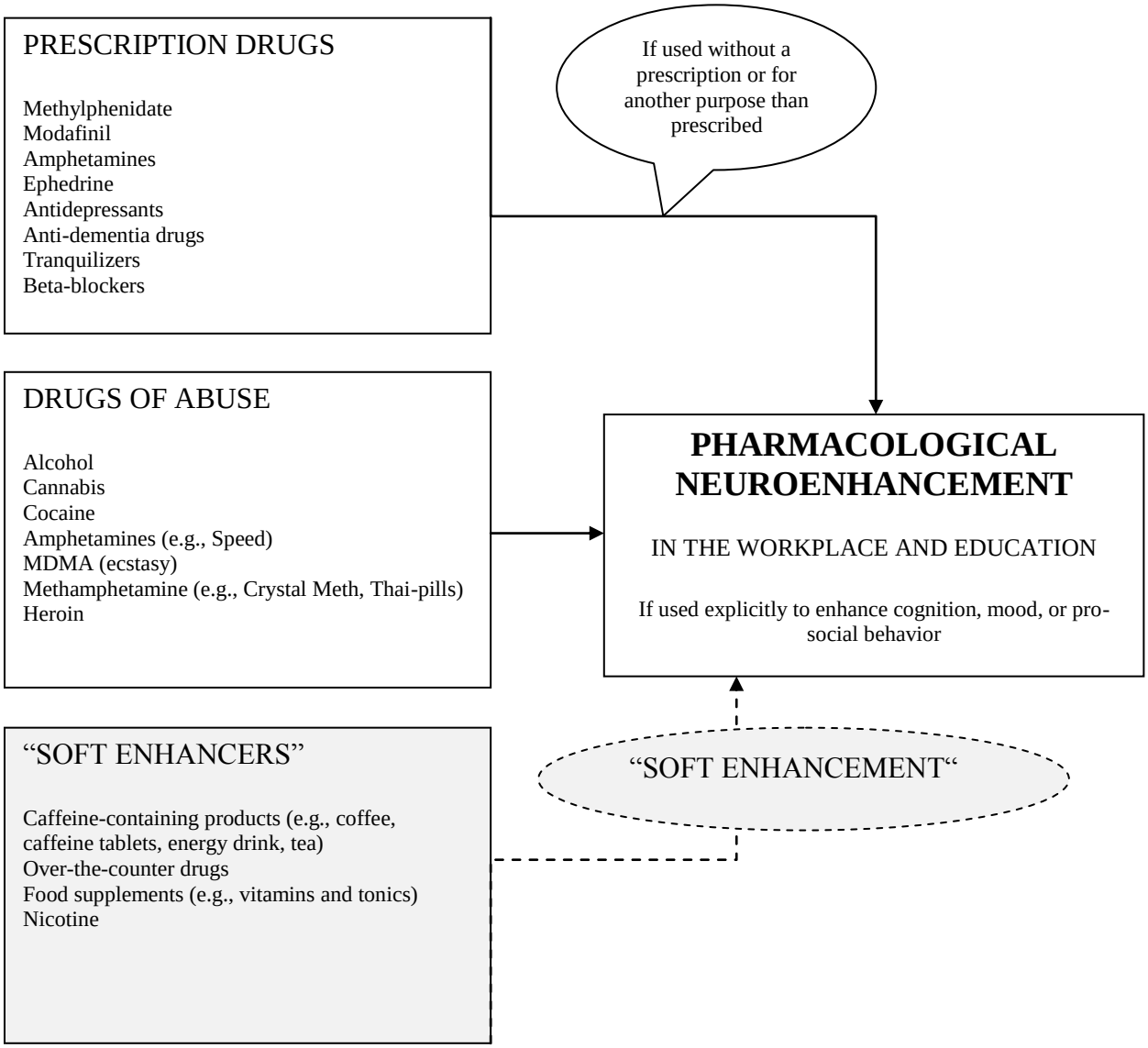

Figure 1. The definition of pharmacological neuroenhancement based on users' intention and behavior, and the substances used for cognitive performance enhancement or increased psychological well-being in Europe. The list of substances is not exhaustive (Maier & Schaub, 2015).

Several non-pharmacological alternatives such as cognitive training, mindfulness meditation, transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS) are excluded here despite the fact that they show promising results for cognitive and mood enhancement in healthy individuals (Bostrom & Sandberg, 2009; Coffman, Clark, & Parasuraman, 2014; Dresler et al., 2013; Garland, Hanley, Farb, & Froeliger, 2013). In particular, the approach and the motives for using non-pharmacological enhancement technologies are comparable with pharmacological neuroenhancement.

1.5 Motives for pharmacological neuroenhancement

1.5.1 Cognitive enhancement vs. mood enhancement

Explicit motives for pharmacological neuroenhancement are essential in terms of defining psychoactive substance use as neuroenhancement (see previous section). Depending on the given task and one's current physical and psychological condition, pharmacological neuroenhancement users aim to improve their cognitive function, mood, and/or prosocial behavior (de Jongh et al., 2008). Scientific literature and media focus on pharmacological cognitive enhancement aiming to enhance memory, learning, attention, and vigilance (Farah et al., 2014; Partridge et al., 2011). Enhanced cognitive function is desirable to increase study performance immediately or to augment student's grade point average in the long-term (Greely et al., 2008; Rabiner et al., 2009a). Mui et al. (2013) claim that while well-being and successful social interactions also improve performance at work and in education, they are rarely studied. Presumably because the objective assessment of mood enhancement is difficult and because the absence of a mental disorder is falsely interpreted as happiness and feeling good (Cloninger & Zohar, 2011; Earp, Sandberg, Kahane, & Savulescu, 2014). Why would one who feels good take medication to feel better? The same question asked both for optimal cognition and recreational drug use is likely to reveal more intuitive answers.

1.5.2 Stress and self-efficacy

Due to ever-increasing demands in education, the workplace, and social life, many individuals feel overwhelmed by the amount of work and have to develop new strategies to cope with stress (Lazarus, 1989; Park & Iacocca, 2014). As a consequence of enthusiastic media reports, the use of psychoactive substances or so-called "smart" or "study drugs" (Partridge et al., 2011; Schleim, 2014b) might be perceived as successful stress coping strategy to maintain or improve performance in the short-term (Park & Iacocca, 2014). However, self-efficacy expectations determine the initiation of coping behavior and the efforts invested to manage stress (Bandura, 1977).

Good performance leads to higher self-esteem which is ultimately related to greater happiness (Baumeister, Campbell, Krueger, & Vohs, 2003). People with low self-esteem and low self-efficacy might be more likely to use drugs for pharmacological neuroenhancement to overcome test anxiety or to mitigate perceived weaknesses. Low self-efficacy among individuals who use psychoactive substances as study aids might also explain why neuroenhancement users are less optimistic about their academic success and personal development than non-users (Middendorff et al., 2012). However, people with high self-

esteem are known to be keen to experiment (Baumeister et al., 2003) and might, therefore, also be interested in pharmacological cognitive enhancement.

Moreover, stimulants were found to have beneficial effects on self-regulation and studies suggest that users increase their study efforts after stimulant use independently of a substance's effect (Advokat & Scheithauer, 2013). Thus, even if self-efficacy is low, self-regulation could be improved by stimulants under certain conditions which would justify the prescription misuse. An increase in self-confidence after methylphenidate use was also suggested by an earlier study (Bray et al., 2004). This is likely to occur because recreational stimulants such as cocaine share the same mechanisms of action which results in increased arousal and self-confidence of the users (Müller & Schumann, 2011; Wood et al., 2014). However, overestimation of one's own capabilities can be a further consequence of stimulant use, and healthy individuals show more risky choices after methylphenidate administration, while ADHD patients show no change (Maul & Advokat, 2013).

Bandura's (1986) social cognitive theory states that attainable goals, self-motivation, and controllable outcomes are crucial for self-efficacy and personal development. If individuals perceive pharmacological neuroenhancement as being necessary to achieve their goals, low self-efficacy and repeated neuroenhancement might result (Bavarian et al., 2013). However, the mechanisms of action of certain substances used for cognitive enhancement might have beneficial effects on self-motivation. When effect expectations are fulfilled, the outcome (e.g., good grade) might be perceived as more controllable and repeated pharmacological enhancement is more likely to occur.

1.5.3 Self-medication

Broadly defined, every substance use that follows a certain intention to improve a certain mental or physical state, without being advised by a doctor, would be considered self-medication. Responsible self-medication with indicated over-the-counter drugs for self-recognized conditions is an important element of self-care that can reduce the burden on health care systems (WHO, 1998). However, Khantzians' (1997) self-medication hypothesis of addictive disorders claims that the use of legal and illegal drugs as initially successful self-medication might result in addiction. The addictive potential of drugs used for neuroenhancement, especially psychostimulants, is questionable and depends strongly on dose and frequency of use (Compton & Volkow, 2006). Nevertheless, not the physical but the psychological addiction might be a concern of neuroenhancement drugs because activities can be experienced as more rewarding (Volkow & Swanson, 2008) and one might feel unable to succeed without the drugs (Wulf, Joksimovic, & Tress, 2011). However, pharmacological

neuroenhancement is a form of self-medication somewhere between healthy self-care and addiction. Moreover, it is unclear whether pharmacological neuroenhancement is misuse or self-treatment, especially when used to treat the symptoms of an undiagnosed mental disorder unconsciously (Peterkin, Crone, Sheridan, & Wise, 2011). Self-medication as an explanation model for pharmacological neuroenhancement seems appropriate and necessary to further discuss (Ragan, Bard, & Singh, 2013). The risks of self-medication, such as incorrect drug choice, polydrug use, and associated drug interactions (Ruiz, 2010) have to be discussed in terms of harm reduction. Consideration of these risks is of utmost importance in individuals with mental disorders and co-occurring substance abuse to self-medicate themselves beyond their prescription or to cope with adverse medication effects (Kasten, 1999).

Generally, the pharmacological neuroenhancement is associated with improving some capacity or function beyond the normal ability which was called a functional-augmentative approach to enhancement (Earp et al., 2014). Instead of focusing only on increasing specific functions, Earp et al. (2014) suggested in their welfarist approach to enhancement to focus on biological and psychological changes which increase the quality of life. Therefore, they proposed that diminishment of a higher-order capacity can be a form of enhancement. When reduced neural activity results in reduced emotional intensity of unpleasant or traumatic memories this

1.5.4 Lifestyle choice

In some cases, pharmacological neuroenhancement might be perceived as a lifestyle choice based on own decisions and without having a serious underlying problem that needs to be compensated (Racine & Forlini, 2008). Although pharmacological neuroenhancement often aims to cope with stress, test anxiety, and problems with time management, it is also used by individuals with high baseline performance who want to perform even better (Sahakian & Morein-Zamir, 2011; Sattler & Wiegel, 2013). To maintain a suitable work-life balance is an important topic and improving one’s own grades might be of secondary importance (Hildt et al., 2014; Maier et al., 2013). Being more efficient at work or while studying results in having more time to spend with friends and family. Therefore, pharmacological neuroenhancement might also aim to pass an exam or to finish a work task briefly to invest more time in social relationships. However, because of unknown side effects and long-term effects of psychoactive substances used for pharmacological neuroenhancement and frequent concurrent recreational drug use (McCabe et al., 2014), this lifestyle might not be the healthiest one. Stress might even increase over time instead of being reduced (Wolff, Brand, Baumgarten, Lösel, & Ziegler, 2014).

1.6 Pharmacological neuroenhancement in healthy individuals

1.6.1 Efficacy of pharmacological neuroenhancement in healthy individuals

The efficacy and safety of pharmacological neuroenhancement in healthy individuals is a controversially discussed topic in the current neuroenhancement debate (Bagot & Kaminer, 2014; Farah et al., 2014; Repantis, 2013). While prescription drugs are safe and effective for the indicated treatment of disorders under the supervision of an experienced physician (Rubia et al., 2013), medical safety is not provided for nonmedical use (Wood et al., 2014). Nonmedical use refers to the use of prescription drugs by healthy individuals as well as to the inappropriate use of prescribed medication in patients (Maier & Schaub, 2015; McCabe et al., 2009). In particular, the use of prescription drugs, such as psychostimulants, might affect neuroplasticity and may, therefore, alter cognitive function, behavior, and even the personality of users (Nyberg, 2014).

Positively altered exam outcomes after pharmacological neuroenhancement depend on the neural activity of specific cognitive functions, dose, and task demands (de Jongh et al., 2008; Repantis, Schlattmann, et al., 2010; Wood et al., 2014). Prescription stimulants may lead to an increased function in one cognitive domain, while a second associated cognitive function might be decreased at the same time (de Jongh et al., 2008; Husain & Mehta, 2011). For example, cognitive control increases task performance in simple working memory tasks, but is related to mental inflexibility or compulsivity which could decrease performance in more complex tasks (van der Schaaf et al., 2013). Moreover, the dose-effect-relationship is an important aspect to discuss with regard to several adverse side effects of inappropriate use such as overdose (Wood et al., 2014). Apart from the challenging control of this relationship, resulting health risks such as addiction justify the legal control of such drugs (Dubljević, 2013).

Given that each drug effect is influenced by the drug, set, and setting (Zinberg, 1986), the discussion about effects of pharmacological neuroenhancement has to be extended above the single mechanisms of a potential substance's action. The importance of individual differences in terms of the present physical and mental condition and an individual's environment on the drug's effect cannot be neglected (Zinberg, 1986). When an individual's resources are rather low because of being sleep-deprived, stressed, or suffering from test anxiety, benefits from neuroenhancement use are more likely to occur (de Jongh et al., 2008). Moreover, low baseline performance and genetic predisposition, such as low dopamine levels, are also associated with greater benefits from neuroenhancement (de Jongh et al., 2008; Farah et al., 2014). These differences in an individual's response to pharmacological neuroenhancement

have been described as an inverted U-shape curve (de Jongh et al., 2008). The top of the inverted U symbolizes the optimal intermediate catecholamine level while excessively low or high levels at both ends were associated with impaired cognitive function (de Jongh et al., 2008). Enhancement might, therefore, only be possible if this optimal level has not been achieved yet. Hence, the well-rested, optimally trained brain is difficult to enhance and pharmacological neuroenhancement may then even impair cognition (de Jongh et al., 2008; Quednow, 2010). Due to an individual's responses to prescription drugs and associated undesirable side effects, the use of prescription drugs is only recommended under medical supervision (Dubljević, 2013).

1.6.2 Efficacy of prescription stimulant use in healthy individuals

There is only weak evidence for beneficial effects of pharmacological neuroenhancement with prescription stimulants on cognition (Farah et al., 2014; Repantis, 2013). Methylphenidate, the drug most commonly used for neuroenhancement, elevates the neurotransmission of dopamine and noradrenalin by reuptake inhibition at the respective monoamine transporters (Mehta, Sahakian, & Robbins, 2001; Wood et al., 2014). Thus, it is assumed to influence the cognitive domains of executive functions and working memory in healthy individuals (Repantis, 2013; Smith & Farah, 2011; Wood et al., 2014).

A placebo-controlled study among young healthy men found improved working memory and planning skills after methylphenidate administration (Elliott et al., 1997). However, this effect was, limited to novel tasks and even impaired cognitive function was found in previously established performance. A study with healthy, sleep-deprived adolescents revealed no cognitive test performance effects after the administration of methylphenidate (Bray et al., 2004). A further study with methylphenidate administration in healthy individuals showed a selective enhancement of declarative memory consolidation after the administration of 20 and 40 mg (Linssen, Vuurman, Sambeth, & Riedel, 2012). An increased concentration, alertness, and emotional tension as well as a slightly euphoric effect was found after administration of 60 mg methylphenidate (Hysek et al., 2014). A recent study on the effects of a standard dose of mixed amphetamine salts found no cognition-enhancing effects when a standard clinical dose was used (Ilieva & Farah, 2013). However, students who used Adderall® as study aid reported a positive influence on mood, energy, and motivation (Vrecko, 2013). They reported that though the drug did not make them smarter, work was made more pleasant.

Nevertheless, recent research suggests that changes in emotion and motivation levels caused by drug administration, regardless of the drug's effect, affect mental performance

(Mommaerts et al., 2013; Vrecko, 2013). In a double-blind placebo-controlled study, sleep deprived participants who assumed themselves to have used methylphenidate performed better in a word recall task independent of having received the prescription drug or the placebo (Mommaerts et al., 2013). Moreover, methylphenidate improved reward versus punishment learning in individuals with high baseline performance of working memory, while low-working memory at baseline was associated with impaired learning after methylphenidate administration (van der Schaaf et al., 2013). The occasional nonmedical oral use of methylphenidate in low doses seems not to be harmful despite side effects, such as sleep disorders, tachycardia, headache, sweating, or loss of appetite can occur (Bruggisser et al., 2012). However, frequent nonmedical stimulant use and non-oral use was associated with depressive symptoms (Teter, Falone, Cranford, Boyd, & McCabe, 2010). Moreover, since recreational stimulant use has been associated with deficits in the cognitive domains of attention, executive functions as well as working and long-term memory (Vonmoos, Hulka, Preller, Jenni, Baumgartner, et al., 2013), prescription stimulant use might also be associated with cognitive deficits.

1.6.3 Efficacy of other drug use in healthy individuals

Furthermore, modafinil showed inconsistent effects on cognitive functions. A single dose of 200 mg of modafinil had strong effects on executive function and memory among sleep-deprived individuals but, contrarily, induced drowsiness among well-rested participants (Repantis, Schlattmann, et al., 2010). Modafinil can increase attention and vigilance but has no effect on the general cognitive abilities (Gilleen et al., 2014). Moreover, the effect of modafinil is believed to be baseline dependent, which means that only students with low intelligence quotients benefit from using (Randall, Shneerson, & File, 2005). Furthermore, studies found no effect of antidepressants use in healthy individuals (Repantis et al., 2009) and the cognition-enhancing effects of anti-dementia drugs are questionable due to specific testing situations (e.g., flight simulators; Wade et al., 2014; Yesavage et al., 2002).

Thus, the translation of study findings from single dose applications within laboratory studies to real life consumption is difficult (Schleim, 2014a). However, these findings help identify potential effects and side effects of nonmedical use of controlled prescription drugs. The prediction of cognitive or mood enhancing effects as well as adverse affects is more difficult when using alcohol or illegal drugs or both simultaneously. The initial state of euphoria might suddenly change and initial beneficial effects can transform into undesired intoxication (Maier & Schaub, 2015). Moreover, the unknown ingredients of illegally

purchased drugs allow no prediction of the drug's effect, which in turn, depends even more on set and setting (Zinberg, 1986) than prescription drug use.

1.6.4 Personality

Pharmacological neuroenhancement might alter personality while, on the other hand, personality is assumed to influence the willingness to use pharmacological neuroenhancement. Critics of pharmacological neuroenhancement raise concerns about the users authenticity and claim that one's personality might change in an undesirable way as a consequence of chronic illicit use (de Jongh et al., 2008). However, studies found that pharmacological neuroenhancement was associated positively with sensation seeking, impulsivity, neuroticism, aggression, and negatively with consciousness (Middendorff et al., 2012; Rabiner et al., 2009a; Weyandt et al., 2013). Moreover, the individual variability in baseline levels of dopamine is closely related to personality traits such as impulsiveness (van der Schaaf et al., 2013). Impulsive individuals benefit the strongest from stimulant use as similar to ADHD patients that reduce impulsivity symptoms medically (Smith & Farah, 2011). Recreational stimulant users revealed higher levels of self-reported impulsivity and showed novelty seeking and more ADHD symptoms compared to stimulant-naïve controls (Vonmoos, Hulka, Preller, Jenni, Baumgartner, et al., 2013; Vonmoos, Hulka, Preller, Jenni, Schulz, et al., 2013). Additionally, recreational stimulant users behaved less prosocial and less empathic, showed deficits in theory of mind, and reported having a smaller social network (Hulka et al., 2014; Preller, Hulka, et al., 2014). Studies considering the nonmedical use of methylphenidate in healthy individuals have only addressed acute methylphenidate effects on social cognition and behavior (Hysek et al., 2014; Schmid et al., 2014) while the effects of chronic use on social behavior are largely unknown.

Nevertheless, Quednow (2010) proposed that particularly narcissistic and ambitious people might be more interested in pharmacological cognitive enhancement. Narcissists have a grandiose view of their self and high self-esteem (Baumeister et al., 2003). Both high and low self-esteem can lead to alienating others because of difficulties with interpersonal interactions (Baumeister et al., 2003). Research on the so-called "dark triad" of personality traits has revealed that subclinical narcissism is closely related to Machiavellianism and subclinical psychopathy (Rauthmann & Kolar, 2012) Manipulative, opportunistic, and antisocial behavior might, therefore, be potential personality features of pharmacological cognitive enhancement users as well.

1.7 Ethical and legal considerations

The bioethical debate on neuroenhancement focused mainly on the use of psychoactive substances for cognitive enhancement in healthy individuals and has discussed the ethics of cognitive enhancement in-depth (Bostrom & Sandberg, 2009; Farah et al., 2004; Maslen, Faulmüller, & Savulescu, 2014; Sahakian & Morein-Zamir, 2007). In particular, the most discussed topics were the safety of drugs used for cognitive enhancement and potential inequalities which might develop or exaggerate, given that an effective and safe drug would be brought to market. Nevertheless, Advokat and Scheithauer (2013) claimed that medical and legal consequences of cognitive enhancement use are often underappreciated in the ethical debate.

Sahakian and Morein-Zamir (2007) raised four concerns regarding the use of potentially cognition-enhancing drugs which were confirmed by the *Nature* readership who participated in the journal's poll about cognitive enhancement (Maher, 2008). Respondents were afraid of potential side effects of nonmedical prescription drug use and unknown risk of addiction, of drug-induced changes in personality, of peer pressure to use such drugs, and of inequality regarding the accessibility of drugs for cognitive enhancement (Maher, 2008).

However, Greely et al. (2008) called for an evidence-based approach considering the risks and benefits of potentially cognition-enhancing drugs and argued that healthy adults should decide for themselves whether or not to engage in pharmacological cognitive enhancement. Adults are, in fact, assumed to be responsible for their health state but drug abuse and addiction as a resulting worst case scenario of neuroenhancement might diminish their ability to decide rationally (Dubljević, 2013). Nevertheless, Greely et al. (2008) suggested that cognitive enhancement with methylphenidate, modafinil, and amphetamines is already common and would even increase in the near future (Greely et al., 2008). This publication has been followed by lots of criticism because of the poor quality of evidence of their statements (Lucke, Bell, Partridge, & Hall, 2011b; Outram, 2010).

Nevertheless, there were also positive reactions and two directions of bioethical thinking about neuroenhancement were established. While some researchers investigated the dangers of cognitive enhancement on the individual level and resulting potential negative consequences for the society (Outram, 2010), others focused on potential benefits for personal development and economic gain for society (Greely, 2013; Greely et al., 2008). Both sides addressed normative questions about the regulation and accessibility of cognition-enhancing drugs for healthy individuals. However, the whole bioethical debate has been based on the assumptions that the use of prescription stimulants for cognitive enhancement is prevalent and

will spread in the near future and that a more or less safe and effective cognition-enhancing drug will be developed (Greely et al., 2008; Sahakian & Morein-Zamir, 2007). Schleim and Quednow (2015) subsequently termed these assumptions as neuroenhancement prevalence hypothesis and neuroenhancement optimism hypothesis. Moreover, Quednow (2010) questioned the need of a debate on a technology that will probably never be realized and supposed further that only a specific personality type would show interest in pharmacological cognitive enhancement. This would not support the prediction of an increase of cognitive enhancement among healthy individuals.

Despite the lack of evidence for effective and safe cognition-enhancing drugs, pharmacological cognitive enhancement is seen as cheating, and it is assumed that individuals might be coerced to use them if other's would do so as well (Maslen et al., 2014). Hence, the bioethical debate strengthens the importance of scientific research on neuroenhancement (Maslen et al., 2014) but no clear recommendations for regulations are phrased. However, Dubljević (2013) argued that a moderate permissible regulation of enhancement stimulants might be most appropriate. He compared the use of methylphenidate and other drugs and rejected the idea that methylphenidate might act as gateway to illegal drug use, which had been an argument for prohibition. Nevertheless, he emphasized the danger profile of prescription stimulants which legitimates that these drugs are controlled by the narcotics law and require a physician's prescription.

The nonmedical use of prescription drugs for cognitive enhancement has received attention in policies across the world. It was first discussed in the U.S. Presidents Council on Bioethics in 2003 with regard to the distinction between therapy and enhancement, which still remains an ethically unsolved issue (Maslen et al., 2014). Moreover, the UK Parliament released a brief report addressing the use of prescription drugs for cognitive enhancement in which concerns about possible regulations were raised (POST, 2007). Furthermore, the Italian National Bioethics Commission has discussed the development of cognitive enhancement use without having a solution, however, addressing the often mentioned concerns of fairness, merit, safety and coercion (CNB, 2013). A similar Swiss report has labeled trade-offs between justifiable and illegal human enhancement and predicted future development of enhancing technologies for the first time (Eckhardt, Bachmann, Marti, Rütsche, & Telser, 2011).

The awareness of pharmacological neuroenhancement in Switzerland and its impact on public health was raised and debated in policy even before evidence-based data on neuroenhancement in Switzerland were available. In 2009, a female Swiss politician submitted a postulate to the Swiss National Council proposing that the Swiss Federal Council

should conduct a study on the nonmedical prescription drug use for cognitive enhancement. In her letter, she pointed out that stimulant prescriptions were increasing, that Novartis planned to introduce 600 new medications for cognitive enhancement, and that drug dependency is rarely investigated in Switzerland despite being a big public health issue (Fehr, 2009). The Swiss Federal Council accepted the postulate and announced a report for 2011 which was finally published in May 2014 (Eckhardt, 2014). The report identified potential misuse of ADHD medications for neuroenhancement and suggested the implementation of guidelines for Swiss practitioners. Furthermore, a public information campaign on ADHD and methylphenidate use was recommended (Eckhardt, 2014). However, based on this report the Swiss Federal Council announced in a media release at the end of 2014 that there is currently no need for additional regulations of the prescription of ADHD medications in Switzerland. The well-reasoned conclusion was drawn, inter alia, taking into consideration our study findings on neuroenhancement among Swiss students (Maier et al., 2013) and on neuroenhancement in the Swiss general population (Maier & Schaub, 2014). The findings of the latter study will be presented and interpreted in-depth in the first two original research articles of the present thesis.

1.8 Overview of the original research

Having reached the conclusion that pharmacological neuroenhancement is prevalent among Swiss university students (Maier et al., 2013), we were interested in the current situation concerning neuroenhancement in the general population. As mentioned above, only one non-representative study investigated substance use to improve cognitive performance or mood at work among Swiss employees, and revealed a past-year prevalence of 4% (Grebner et al., 2010). Unfortunately, the authors missed to specify the substances used and it was, hence, unclear whether this number only reflected the use of freely available or also medically indicated substances which would not be considered for neuroenhancement. The previously mentioned study among German employees found a past-year prevalence of 5% but regular use was rare (Kordt, 2009). Nevertheless, psychoactive substance use at work is associated with risks of impaired instead of enhanced cognition and might cause accidents or negative health consequences. The Swiss Accident Insurance Fund (SUVA) has launched a project called Progrès, aiming to address the increase in occupational illness as a consequence of exposure to risk factors at work. Impaired mental health as a consequence of chronic stress or substance use to cope with stress is associated with high costs for the healthcare system. This constitutes the need for early detection and early prevention of impaired mental health and

trends in unhealthy behavior. Within this project, SUVA funded the first representative study on pharmacological enhancement at work and in education, which we conducted in 2013.

Following our feasibility study conducted to implement the most appropriate survey on pharmacological neuroenhancement in Switzerland (Schaub & Maier, 2012), we administered a questionnaire which contained items regarding socio-demographic data, stress at work and in education, physical and mental health, and psychoactive substance use. We used pictures to present packages, blister packs, and pills of the prescription and over-the-counter drugs mentioned in the survey to facilitate user's recognition and hypothesized

1 a) that the lifetime prevalence of pharmacological neuroenhancement in the Swiss general population was lower than 5%,

1 b) that pharmacological neuroenhancement was associated with higher levels of stress and more illegal drug use,

1 c) that ADHD medications are the most commonly used neuroenhancers,

1 d) and that alcohol and cannabis users would not respond positive to the neuroenhancement items even if they were using these psychoactive drugs optional for direct or indirect enhancement purposes.

German experts rated stress at work and the new normal of the 24 hours society as the most causal factors for neuroenhancement (Kordt, 2009). In addition, stress at work or in education has been the most prominently discussed reason for pharmacological neuroenhancement (Siegrist & Rödel, 2006; Wolff & Brand, 2013). Moreover, the first Swiss studies on pharmacological neuroenhancement confirmed the positive relationship between stress and substance use for cognitive enhancement (Deline et al., 2014; Grebner et al., 2010; Maier et al., 2013; Ott & Biller-Andorno, 2014). Thus, we were interested in how much variance of psychoactive substance use for cognitive and mood enhancement in the past 12 months would be explained by stress at work and in education in a prediction model. The interpretation of stress at work is closely related to available coping strategies (Lazarus, 1989) and self-efficacy expectations (Bandura, 1982) as discussed in the section on motives for pharmacological neuroenhancement. Pharmacological neuroenhancement in healthy individuals as a strategy to cope with stress, however, is a form of *moderate self-medication* and the substances used are functional means to reduce stress and to improve performance under stress (Wolff et al., 2014). This was the first study to introduce the concept of self-medication in order to investigate pharmacological neuroenhancement. It seemed reasonable

to include such a strong construct in the thesis, because it is suitable to explain the behavior of pharmacological neuroenhancement users concisely. Furthermore, the construct of self-medication enables an open dialogue about risks of pharmacological neuroenhancement beyond the mechanisms of action of single substances used (Kasten, 1999).

We included individuals with a current or past mental health disorder such as ADHD, narcolepsy, or depression in the study. We assumed that some might misuse their prescription drugs indicated for the treatment of their mental disorder for neuroenhancement purposes. In addition, we suggested that they might report the nonmedical use of further prescription drugs or other illegal psychoactive substances to improve performance at work or while studying. This additional substance use was proposed to reduce symptoms and side effects of their mental disorder or their prescribed medication (Kasten, 1999) as *serious self-medication*. Although cognition-enhancing drugs were developed to treat cognitive deficits and improve quality of life for individuals with a mental disorder (Sahakian & Morein-Zamir, 2007), the nonmedical use of those drugs among healthy individuals became the main focus of the neuroenhancement debate. Individuals with a mental disorder were often excluded from studies without considering that they might enhance themselves beyond their prescribed medication (Frauger et al., 2011; Jardin, Looby, & Earleywine, 2011; Maier & Schaub, 2015). In the second study of the thesis, we investigated the importance of stress, self-efficacy, and mental health as prediction models for pharmacological cognitive enhancement and mood enhancement independently. We hypothesized that both forms were associated with

2 a) stress and long-term stress (*moderate self-medication*),
2 b) illegal drug use (*moderate self-medication*),
2 c) and mental disorders (*serious self-medication*).

2 d) Further hypotheses were, that cognitive enhancement is associated with time pressure and other negative professional or academic stressors (*moderate self-medication*)
2e) and that mood enhancement is associated with low self-efficacy (*moderate self-medication*).

The first two studies aimed to provide the most representative monitoring of nonmedical prescription and other illegal drug use for pharmacological neuroenhancement in Switzerland, to identify motives for and predictors of pharmacological neuroenhancement, and to make

implications for policy, prevention or intervention if required. While these two studies had focused on a broad range of potential enhancement situations, we had a special interest in the consequences of cognitive enhancement in healthy individuals. Therefore, we examined cognitive and social cognitive differences between healthy individuals who used methylphenidate (Ritalin®) for cognitive enhancement on a regular basis and stimulant-naïve controls. Prescription stimulants such as methylphenidate share similar mechanisms of action with illegal drugs such as cocaine (Wood et al., 2014). As studies revealed impaired cognitive functions and altered social cognition in recreational stimulant users (Preller, Hulka, et al., 2014; Vonmoos, Hulka, Preller, Jenni, Baumgartner, et al., 2013), we hypothesized

3 a) that healthy recently abstinent cognitive enhancement users perform worse in cognitive tasks than stimulant-naïve controls,

3 b) that healthy recently abstinent cognitive enhancement users behave more self-serving, less prosocial and less empathic in social interactions compared to controls,

3 c) that the personality profile of regular cognitive enhancement users was similar to recreational stimulant users and, therefore, highly impulsive,

3 d) and that healthy cognitive enhancement users show the dark triad personality traits: narcissism, Machiavellianism, and psychopathy.

Along with the careful consideration of the scientific literature on pharmacological neuroenhancement, the general introduction faced several relevant topics and investigated not only the prevalence in Switzerland, but also the motives for use (Wolff et al., 2014). The following original research articles address every mentioned issue and provide a substantial contribution to the current neuroenhancement debate on various levels.

2 Prevalence of and motives for pharmacological neuroenhancement in Switzerland - results from a national Internet panel

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Author contributions

MPS and LJM designed the study based on the findings of their previous feasibility study on pharmacological neuroenhancement in Switzerland. LJM took photographs of all prescription drugs and over-the-counter drugs which were presented to the participants together with the survey questions. MPS and LJM collaborated with the LINK institute to implement, pilot, and validate the online survey, and to collect the data. The LINK institute provided some preliminary descriptive results. LJM analyzed and interpreted the data, and drafted the manuscript. MPS and SH reviewed the manuscript and provided methodological suggestions, and LJM revised the manuscript accordingly.

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2.1 Abstract

Aims: To estimate the prevalence of self-reported pharmacological neuroenhancement (PNE) with prescription or recreational drugs among the Swiss general population and correlates of PNE. **Design:** A population-based cross-sectional study using a self-administered online survey. **Setting:** A telephone-recruited highly representative Internet Panel in Switzerland. **Participants:** A total of 10 171 Swiss employees and students (unweighted *N* = 10 084) aged 15 to 74 years (mean age: 39.1 ± 13.3; 46.6% female). **Measurements:** Self-reported lifetime, past-year, and past-month use of prescription or recreational drugs for PNE, motives for use, and correlates of PNE including socio-demographic, health, and recreational drug use characteristics. **Findings:** The lifetime prevalence of PNE was 4.0% (95% CI = 3.62, 4.38), and the past-year prevalence was 2.1% (95% CI = 1.82, 2.38). Lifetime pharmacological mood enhancement (3.1%; 95% CI = 2.76, 3.44) was more prevalent than pharmacological cognitive enhancement (1.4%; 95% CI = 1.17, 1.63). Fifty-four participants reported both (0.5%; 95% CI = 0.36, 0.64). PNE was associated with studying rather than full-time (OR = 0.35; 95% CI = 0.21, 0.57) or part-time employment (OR = 0.39; 95% CI = 0.23, 0.67), stress (OR = 1.51 95% CI = 1.31, 1.75), cocaine (OR = 2.40; 95% CI = 1.51, 3.82) and amphetamine use (OR = 2.44; CI 95% = 1.37, 4.33), diagnosis of a mental disorder (OR = 4.26; 95% CI = 3.14, 5.80), and perceived poor health (OR = 0.76; 95% CI = 0.64, 0.90). **Conclusions:** Pharmacological neuroenhancement was rare among Swiss employees and students (4.0%). Pharmacological mood enhancement (3.1%) is more prevalent than direct cognitive enhancement (1.4%).

Key reference terms: Pharmacological neuroenhancement; cognitive enhancement; mood enhancement; nonmedical prescription drug use; illegal drug use

2.2 Introduction

The use of prescription or recreational drugs by healthy individuals to enhance cognitive or affective function (de Jongh et al., 2008; Repantis, 2013) is termed pharmacological neuroenhancement (PNE) when explicitly used for the purpose of improved performance at work or in education (Maier & Schaub, 2015). Prescription drugs indicated for the treatment of psychiatric disorders such as attention-deficit hyperactivity disorder (ADD/ADHD) or narcolepsy are the focus of the PNE debate because these drugs also have cognitive-enhancing effects in healthy individuals (Husain & Mehta, 2011; Repantis, 2013).

The prevalence of nonmedical stimulant use is well researched among American college students although differentiation of motives for use is often lacking (Arria & DuPont, 2010; DeSantis et al., 2008; McCabe et al., 2005, 2014; Weyandt et al., 2013). While the estimated annual prevalence of drug use for PNE was 4.0% (Sussman et al., 2006), estimated nonmedical use ranged from 1.5% to 35% (Bogle & Smith, 2009; Wilens et al., 2008). The most recent and most comprehensive review estimated the rate of prescription stimulant misuse among college students at 17.0% (Benson, Flory, Humphreys, & Lee, 2015). Table 1 provides an overview of recently published studies estimating specifically the prevalence of PNE among different study samples and different substances used to improve performance at work or while studying.

Table 1. Studies estimating the prevalence of pharmacological neuroenhancement (PNE) published between 2000 and 2015; only PNE specific studies are included in the table. Please refer to Benson et al. (2015) for a general overview of studies estimating the prevalence of nonmedical prescription stimulant misuse.

Author (Year)	*Study sample*	*Lifetime prevalence of PNE*		*12-month prevalence of PNE (or other if specified)*		*Prevalence soft enhancement*
		Prescription drugs (nonmedical use)	*Recreational drugs (for enhancement)*	*Prescription drugs (nonmedical use)*	*Recreational drugs (for enhancement)*	*Caffeine, food supplements, OTC-drugs*
(Arria et al., 2013)	984 U.S. college students	38.0% stimulants to help study at least once in 4 years				
(Castaldi et al., 2012)	77 Italian university students (limitation: unclear whether OTC drugs are included)	16.0% – drugs to improve attention, cognitive performance or memory or to cope with fatigue and sleepiness				
(DAK, 2009)	3017 German employees aged 20 to 50 years old	1.0% to 5.0% MPH, MOD, ATD, BB, or ADEM to improve performance at work		2.2% regular users		
(DAK, 2015)	5017 German employees aged 20 to 50 years old	6.7% MPH, MOD, ATD, BB, or ADEM to improve performance at work 3.3% cognition 4.7% mood and reduced nervousness		4.2% regular users 3.2% – all 1.5% cognition 2.1% mood and reduced nervousness		
(DeSantis et al., 2008)	1811 U.S. college students	23.2% stimulants to stay awake to study 21.5% stimulants to concentrate on your work 11.8% stimulants to help memorize Any purpose:				

		34.0% stimulants				
(Dietz et al., 2013)	2569 German university students			20.0% – all (RRT) [a]		
(Eickenhorst et al., 2012)	1218 German university students and 106 German graduates	7.0% illicit drugs – MPH, MOD, DEX, ATD, BB, COC, HER, or MDMA				*Lifetime* 89.3% COF [c] 25.2% HSED 11.1% CAFT
(Forlini, Schildmann, Roser, Beranek, & Vollmann, 2015)	1026 German university students	2.2% – drugs to enhance attention, endurance, and cognitive function	3.8% CAN 1.4% AMPH 1.3% COC 1.0% MDMA			*Lifetime* 55.9% COF 40.8% ED
(Franke, Bonertz, et al., 2011; Franke, Christmann, et al., 2011)	1035 German high school and 512 German undergraduate university students	1.3% stimulants – all	2.6% illegal stimulants	0.3% stimulants – all < 0.1% – all (*30 d*)	1.0% illegal stimulants 0.3% – all (*30 d*)	*Lifetime/12 m/30 d* 53.2%/8.5%/6.3% COF 39.0%/10.7%/6.3% ED 10.5%/3.8%/0.8% CAFT
(Franke et al., 2013)	1145 German surgeons	8.9% illicit drugs – all (vs. 19.9% RRT) 2.6% DEX 2.5% MPH 2.2% MOD 2.4% ATD (vs. 15.1% RRT) 1.6% COC 1.2% EPH 0.9% AMPH 0.6% MDMA 0.6% ATX 0.3% ADEM		3.0% illicit drugs – all 1.4% illicit drugs – all (*30 d*) 0.8% illicit drugs – all (*7 d*) 1.0% ATD 0.5% ATD (*30 d*) 0.4% ATD (*7 d*)		
Franke et al. (2014)	3306 surgeons at international conferences					*Lifetime/12 m* 66.8%/61.9% COF 24.2%/15.4% ED 12.6%/5.9% CAFT *30 d/7 d* 56.9%/50.5% COF 9.9%/6.1% ED

						4.7%/3.8% CAFT
(Gay, Houdoyer, & Rouzaud, 2008)	663 French employees	24.1% – all	7.5% ALC 2.1% CAN			*Lifetime* 10.3% NIC
(Grebner et al., 2010)	1004 Swiss employees			4.0% drugs to improve cognitive performance or mood at work 10.0% drugs to relax or sleep after stress at work (to work better the next day)		
(Mache et al., 2012)	1053 German university students	1.0–13.0% illicit drugs – all 15.0% CAN [b] 2.3% COC 2.2% MPH 2.0% BB 1.0% MOD 1.0% FLX 0.1% PIR				*Lifetime* 22.0% HSED 10.0% CAFT
(Maher, 2008)	1427 academics from 60 countries	20.0% – all 12.4% MPH 8.8% MOD 6.0% DEX & other 3.0% BB				
(Maier et al., 2013)	6275 Swiss university students	7.8% – all 4.1% MPH 2.7% SED/SLP 1.2% BB 0.5% ATD 0.3% MOD 0.1% ADEM	7.6% – all 5.6% ALC 2.5% CAN 0.4% AMPH 0.2% COC 0.1% MDMA 0% GHB/GBL	*30 d prior to last exam* 2.6% MPH 2.1% SED/SLP 0.7% BB 0.4% ATD 0.2% MOD 0.1% ADEM	*30 d prior to last exam* 5.1% ALC 1.8% CAN 0.3% AMPH 0.1% COC 0.02% MDMA 0% GHB/GBL	*Lifetime/30 d prior to last exam* 53.2%/49.1% COF 35.9%/29.7% ED 18.2%/14.9% VT 18.2%/13.2% HSED 4.4%/2.6% CAFT
(Mazanov, Dunn, Connor, & Fielding, 2013)	1729 Australian university students	1.9% MOD/RAC to study 4.4% MPH/DEX to study 1.5% SED to study	4.5% illegal drugs to study			*Lifetime/* 63.5% CAF 22.0% OTC
(McNiel et al., 2011)	243 U.S. dental & dental hygiene	8.2% stimulants to improve attention/				

	students	concentration 1.6% stimulants for higher grades DEX > MPH			
(Middendorff et al., 2012)	7989 German university students	5.3% illicit drugs – all 1.3% various drugs 1.2% CAN 1.0% MPH 0.6% BB 0.5% AMPH 0.2% MOD 0.2% COC 0.1% MDMA			*Lifetime* 5.2% – all [d] 4.3% HSED [d] 0.8% CAF [d]
(Ott & Biller-Andorno, 2014)	1765 Swiss university students	4.7% ADHD drugs to help study MPH < MOD < DEX			
(Partridge, Lucke, & Hall, 2012)	1265 Australian university students	2.4% drugs to enhance concentration and alertness			
(Prudhomme White, Becker-Blease, & Grace-Bishop, 2010)	1025 U.S. university students	8.7% MPH to improve study habits 3.2% MPH to improve grades Any purpose: 16.2% stimulants			
(Rosiers & Van Hal, 2010)	1501 Flemish university and college students			2.9% stimulants 2.6% stimulants (*exams*)	
(Sattler & Wiegel, 2013)	5882 German university students	4.6% drugs to enhance the cognitive efficiency		3.2% – all 2.3% – all (*6 m*) 1.2% – all (*30 d*)	
(Schelle et al., 2015)	1572 Dutch university students	1.7% drugs to improve cognitive function	1.3% illegal drugs 1.8% ALC [e]		*Lifetime* 45.6% – all [e] 41.7% CAF 9.0% OTC

						3.0% NIC 0.5% SMA [f]
(Schilling, Hoebel, Müters, & Lange, 2012)	6142 German participants (any)				1.5% illicit drugs – all 1.2% ATD 0.5% AMPH 0.1% BB	
(Singh et al., 2014)	877 UK university students	6.2% MOD 4.0% MPH 2.0% ADD				*Lifetime* 24.3% CAFT
(Teter, McCabe, LaGrange, Cranford, & Boyd, 2006)	4580 U.S. college students	5.4% stimulants to concentrate 5.0% stimulants to study 4.0% stimulants to increase alertness DEX > MPH Any purpose: 8.3% stimulants		Any purpose: 5.9% stimulants – all 4.5% DEX 1.4% MPH		
(Timmer & Glas, 2012)	422 Dutch psychiatrists and doctors working in psychiatry			11.0% – all 5.0% BZD 4.0% BB 2.0% MPH		
(Wolff et al., 2014)	1007 German university students	5.8% – drugs to increase cognitive performance	3.5% illegal drugs	3.0% – all	1.7% illegal drugs	*Lifetime/12 m* 83.2%/52.3% – all

[a] Including not only prescription and recreational drugs but also caffeine tablets and should, therefore, be interpreted carefully. [b] The study authors report themselves a prevalence of illicit drug use for PNE of 1.0-13.0% but cannabis use for PNE was reported by 15.0% of participants (Mache et al., 2012). [c] Students reported also the use of the lifestyle drugs, alcohol (83.0%), nicotine (33.0%), and cannabis (14.0%) during their studies, which is not reported in the table, because it refers not to PNE use. [d] Post-coded ("other") and, therefore, underestimated. [e] Alcohol was categorized as lifestyle drug together with nicotine and legally available OTC drugs similar to the category soft enhancement here. However, alcohol is not considered "soft" because the effects and consequences can be compared with those of illegal drugs that are used recreationally. [f] Legal available psychoactive substances that are sold in Smart shops. ADEM: anti-dementia drugs; ADHD: attention-deficit hyperactivity disorder; ALC: alcohol; AMPH: illegal amphetamine; ATD: antidepressants; ATX: atomoxetine; BB: beta-blockers; BZD: benzodiazepines; CAF: products containing caffeine; CAFT: caffeine tablets; CAN: cannabis; COC: cocaine; COF: coffee; DEX: dexamphetamine; ED: energy drinks; EPH: ephedrine; FLX: fluoxetin; GHB/GBL: gamma-hydroxybutyrate/gamma-butyrolactone; HER: heroine; HSED: herbal sedatives; MDMA: 3-4 methylenedioxymethamphetamine (ecstasy); METH: methamphetamine; MOD: modafinil; MPH: methylphenidate; NIC: nicotine; OTC: over-the-

counter drugs; PIR: piracetam; RRT: randomized response technique; SED: sedative medication; SLP: sleeping pills; SMA: legal available products from smart shops; VT: vitamins and tonics.

Several recent studies have concluded that the use of psychoactive substances for cognitive enhancement among students is less prevalent in Europe than in the United States (Castaldi et al., 2012; Eickenhorst et al., 2012; Franke, Bonertz, et al., 2011; Maier & Schaub, 2015; Rosiers & Van Hal, 2010). Three Swiss studies have addressed the prevalence of PNE among students and young Swiss men and reported a lifetime prevalence of PNE of 3.0% to 13.8% but only rare current regular use (Deline et al., 2014; Maier et al., 2013; Ott & Biller-Andorno, 2014). The highest prevalence rate was, however, due to the inclusion of the recreational drugs alcohol and cannabis, which were not only used recreationally (90.2% and 43.3%, respectively) but also to improve study performance (5.6% and 2.5%, respectively) (Maier et al., 2013). Swiss students reported the use of illegal stimulant mainly for recreation (MDMA= 5.2%, cocaine = 4.2%, and amphetamine = 3.7%) and rarely to enhance study performance (all < 0.5%) (Maier et al., 2013) Consistent with previous research (McCabe et al., 2005), all of the Swiss studies observed a positive association between recreational drug use and PNE (Deline et al., 2014; Maier et al., 2013; Ott & Biller-Andorno, 2014). However, the study estimating the prevalence of PNE among young Swiss men is not included in Table 1 because of a lacking predefinition of the purpose of illicit drug use (Deline et al., 2014).Despite an increasing number of research publications on PNE, the generalizability of the research results is problematic because the inclusion of substances used for PNE differs greatly among studies (Maier & Schaub, 2015; Schleim, 2014b). Furthermore, the distinction between medical use and nonmedical use is often not clear. In general, the 12-month prevalence of prescription stimulant use in the Swiss population is low (0.5%) and most prevalent among youth and young adults (Gmel, Notari, & Gmel, 2015). Past-year use of sedative prescription drugs is more prevalent (9.7%) and associated with female gender and increased age (Gmel et al., 2015). Although the source of supply was specified, nonmedical use was not further specified.

Interpreting the results for the prevalence of PNE is also complicated by differences among countries in the approval of medication for the treatment of mental health disorders. Moreover, users are often not aware of the trade names of prescription drugs, and this lack of awareness may bias the outcome of the prevalence of prescription drug use in surveys. A substantial advantage of online surveys is the presentation of pictures of putatively enhancing drugs to facilitate the recognition of the drugs that have been used (Novak et al., 2007). The present study is the first in Europe on the topic of PNE to combine questions about the prevalence of the use of prescription and over-the-counter drugs with pictures of the pills, blister, and packaging. In addition, previous studies of the prevalence of and attitudes toward

PNE have focused primarily on vulnerable groups, such as students (Arria & DuPont, 2010; Franke, Bonertz, et al., 2011; Rabiner et al., 2009a; Weyandt et al., 2013), scientists (Maher, 2008), physicians (Merlo, Singhakant, Cummings, & Cottler, 2013), and pilots (Mumenthaler et al., 2003; Yesavage et al., 2002), but never on the general population.

This study was designed 1) to estimate the prevalence of PNE among employees and students in Switzerland considering different motives for use; 2) to identify relevant substances used for direct cognitive enhancement (PCE) or increased psychological well-being and mood enhancement (PME); and 3) to investigate the differences between people experienced with PNE and non-users to reveal potential predictors for PNE.

2.3 Materials and methods

2.3.1 Participants and enrollment procedure

Participants were drawn from a representative Internet panel of the LINK institute for market and social research in Switzerland, which consists of more than 130 000 people living in Switzerland who consented to be contacted for public opinion surveys administered through the Internet. The LINK institute uses a computer-assisted telephone interviewing system to recruit panelists representing the Swiss general public. These panelists are representative of the 15- to 74-year-old population of Switzerland that uses the Internet at least once per week for private purposes and is able to answer a questionnaire in German, French, or Italian. The study was conducted during March 2013, and participants were rewarded with one of the following incentives, equal to a value of approximately 2 Euros: points for supermarkets, bookshops, or donation campaigns.

A total of 39 996 e-mail invitations were sent out, and 18 094 began the survey, corresponding to approximately 45.2% of the invitations. Of the 18 094 panelists who responded, 12 404 met the eligibility criteria (currently employed or in education and quota not yet fulfilled) for the study. A total of 10 084 (82.3%) completed the survey; 2320 (18.7%) did not complete the survey (see participant flow diagram; Fig. 2).

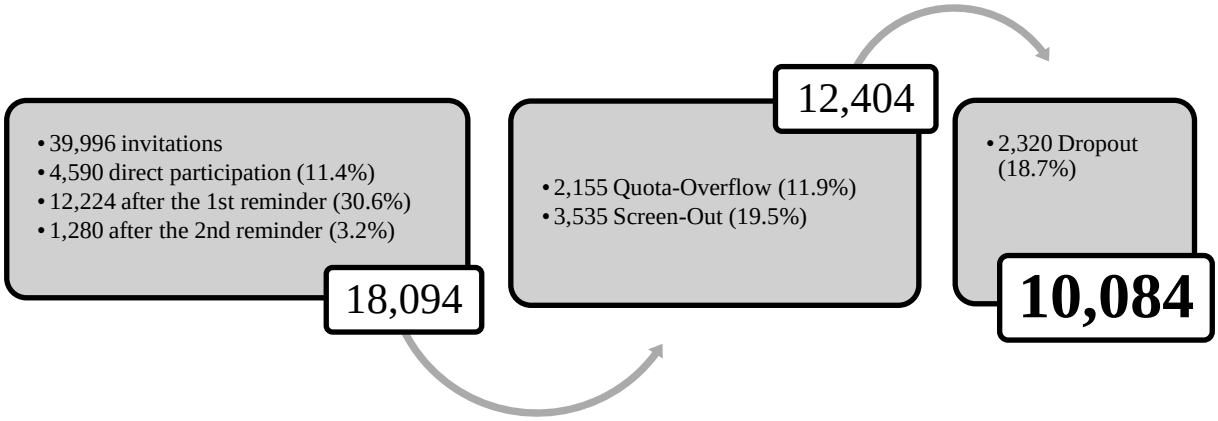

Figure 2. Flowchart of the sample composition using the Swiss Internet panel of the LINK institute.

The self-reported data on PNE and correlates were weighted for age, gender, and language region to create national-level estimates of the prevalence of neuroenhancement. The definition of quota cells for the sample was based on the data for the constant resident population of Switzerland (STATPOP) published by the Federal Statistical Office. Informed consent was obtained from all participants included in the study. The final weighted sample referred to in the present paper consisted of 10 171 participants; the number of interviews realized per quota cell and the resulting weighting factor for the data for each language region in Switzerland are provided in the supplementary materials (Table S1).

2.3.2 Outcome measures

A self-administered online questionnaire based on previous surveys of substance use at work or while studying was used to estimate the prevalence of PNE as well as important correlates such as socio-demographic data, stress, and physical and mental health; the specifications of the questionnaire design are provided in the supplementary materials (Methods S1). The questionnaire was pretested with 103 participants of the LINK Internet panel and improved accordingly.

Participants were asked whether they were aware of PNE and whether they knew other people using prescription or recreational drugs intentionally to enhance cognition or mood at work or while studying. The prevalence of and the two main motives for PNE at work or for studying were examined through two principal questions. First, participants were asked

whether they had ever used prescription or recreational drugs to enhance their cognitive performance at work or while studying. Second, they were asked whether they had ever used prescription or recreational drugs to enhance their mood at work or while studying. The group of people who answered affirmatively to at least one of these two questions will be referred to as PNE users hereafter. Cognitive and mood enhancement were the two main motives of interest, but all participants were required to indicate for each substance used whether the use was aimed at specific neuroenhancement purposes: to enhance concentration, alertness, and vigilance; to reduce nervousness; to enhance mood at work or while studying; and to relax after stress at work or in education.

2.3.3 Statistical analysis

Descriptive statistics provided information about the prevalence and substances used for PNE; the prevalence of the use of alcohol, illegal drugs, and legally available soft enhancers; the frequency of stress; and the physical and mental health states of the participants. Initially, we performed separate logistic regression analyses (subsequently termed ‘univariate analyses’) to evaluate the ability of each independent variable to predict the lifetime use of PNE. All predictors from the univariate analyses were entered into a fully adjusted multivariable model. Nagelkerke’s R-square was calculated as a goodness-of-fit measure for the multivariable model. All quantitative analyses were conducted using IBM SPSS Statistics Version 22 (SPSS Inc., Chicago, IL, USA). Significance was set at $P < 0.050$.

2.4 Results

2.4.1 Participant characteristics

The stratified sample displayed an equal distribution of gender (46.5% female) and a mean age of 39.1 years (*SD* = 13.3). The majority of participants were German-speaking and worked full- or part-time. Three of four participants (71.6%) were aware of PNE. One-quarter of the sample was aware of one (14.3%) or more (11.5%) people in their circle of acquaintances who had used prescription or recreational drugs at least once to enhance their cognitive performance (PCE) at work or while studying. One fifth of the participants, however, knew one (11.6%) or more (8.2%) people who had used psychoactive substances to increase psychological well-being (PME) at work or while studying. Participants who knew at least one PNE user (35.0%) were seven times more likely to report own experiences of PNE (OR = 7.03; 95% CI 5.55, 8.90). Moreover, a small number of participants reported that their friends had already recommended PCE (4.3%) or PME (2.3%) to them. A narrow majority of

the sample did not recognize any justification for PNE (57.7%), and only a few people were willing to use prescription drugs (8.7%) or recreational drugs (4.0%) to improve their performance at work or while studying, even if the hypothetical case that the drugs were effective was true. Furthermore, the majority of the participants believed that the use of prescription and recreational drugs for PNE might be harmful (74.3% and 85.3%, respectively).

2.4.2 Prevalence of PNE

The participant characteristics for the analysis of lifetime PNE are presented in Table 2. Of the study participants, 4.0% (n = 411; 95% CI = 3.62, 4.38) reported the use of prescription or recreational drugs to perform better at work or while studying (PNE). Lifetime PME to perform better at work or while studying (3.1%; 95% CI = 2.76, 3.44) was more prevalent than PCE (1.4%; 95% CI = 1.17, 1.63) Fifty-four participants reported both (0.5%; 95% CI = 0.36, 0.64). The past-year prevalence of PNE was 2.1% (n = 215; 95% CI = 1.82, 2.38).

2.4.3 Univariate predictors of lifetime PNE

As shown in Table 2, all variables, except sex, were univariate predictors of lifetime PNE.

Table 2. Participant characteristics of the study population with and without experience with PNE and the odds ratios (OR) for the univariate associations of each variable with lifetime PNE

	Total *N = 10,171*	*PNE* *n = 411*	*No PNE* *n = 9,760*	*OR (95% CI)*	*p*
Sex					
Male	53.4% (5,433)	3.7% (202)	96.3% (5,231)		
Female	46.6% (4,738)	4.4% (208)	95.6% (4,529)	1.19 (0.98–1.45)	.08
Age group					
15-24 years	18.4% (1,876)	5.5% (104)	94.5% (1,772)		
25-34 years	21.1% (2,144)	4.1% (88)	95.9% (2,056)	0.73 (0.55–0.98)	.04
35-44 years	22.1% (2,251)	3.9% (87)	96.1% (2,164)	0.68 (0.51–0.91)	.01
45-74 years	38.3% (3,899)	3.4% (132)	96.6% (3,767)	0.60 (0.46–0.77)	< .01
Linguistic region					
German	73.3% (7,456)	3.8% (285)	96.2% (7,171)		
French	22.6% (2,302)	5.0% (115)	95.0% (2,187)	1.33 (1.06–1.66)	.01
Italian	4.0% (412)	2.4% (10)	97.6% (402)	0.60 (0.31–1.15)	.12
Professional activity					
In education	13.5% (1,375)	6.8% (93)	93.2% (1,282)		
Full-time work ≥ 90%	54.6% (5,553)	3.3% (182)	96.7% (5,371)	0.47 (0.36–0.61)	< .01
Part-time work < 90%	31.9% (3,243)	4.2% (135)	95.8% (3,107)	0.60 (0.46–0.79)	< .01
Monthly income [a]					
< 6000 CHF	25.2% (2,025)	6.0% (122)	94.0% (1,903)		
6000-10 000 CHF	44.2% (3,547)	3.3% (117)	96.7% (3,430)	0.53 (0.41–0.69)	< .01
> 10 000 CHF	30.6% (2,454)	3.6% (89)	96.4% (2,366)	0.58 (0.44–0.77)	< .01
Relationship					
None / temporary	27.4% (2,788)	5.5% (152)	94.5% (2,636)		
Stable	72.6% (7,383)	3.5% (259)	96.5% (7,124)	0.63 (0.51–0.77)	< .01
Children at home <18					
None	64.2% (6,534)	4.6% (299)	95.4% (6,235)		
At least one	35.8% (3,636)	3.1% (111)	96.9% (3,525)	0.66 (0.53–0.82)	< .01
Perceived health					
SF-12, scale 1-5	3.49 (0.79)	3.04 (0.87)	3.50 (0.79)	0.47 (0.41–0.53)	< .01
Stress (12 m)					
SECO, scale 1-5	3.22 (0.94)	3.81 (0.95)	3.20 (0.93)	2.04 (1.83–2.28)	< .01
Psychological consulting					
Never	79.6% (8,091)	1.9% (156)	98.1% (7,935)		
At least once	20.4% (2,080)	12.3% (255)	87.7% (1,825)	7.11 (5.79–8.73)	< .01
Mental disorder [b]					
Never	78.4% (7,970)	1.5% (118)	98.5% (7,852)		
At least one	21.6% (2,201)	13.3% (293)	86.7% (1,908)	10.20 (8.19–12.71)	< .01

Data are % (number) or mean (standard deviation) weighted for age, sex, and language region. [a] No information provided by n = 2,144, all other variables complete. [b] ADD/ADHD, narcolepsy, depression, anxiety disorder, dependency (lifetime diagnosis). PNE: pharmacological neuroenhancement. SECO: State Secretariat for Economic Affairs. SF-12: The 12-Item Short Form Health Survey.

Lifetime use of drugs of abuse and soft enhancers as univariate predictors for PNE are displayed in Table 2. The lifetime use of tobacco, illegal drugs, and over-the-counter (OTC) drugs was more prevalent among PNE users. No association was found for lifetime use of alcohol and caffeine products.

Table 3. Lifetime use of legal and illegal drugs of abuse and potential soft enhancers in the sample and the odds ratios (OR) for the univariate associations of substance use with lifetime PNE

	Total *N = 10,171*	*PNE* *n = 411*	*No PNE* *n = 9,760*	*OR (95% CI)* [a]	*p*
Lifetime drug use					
Alcohol	93.8% (9,541)	95.0% (390)	93.8% (9,151)	1.26 (0.80–2.0)	.32
Tobacco	63.2% (6,424)	76.2% (313)	62.6% (6,111)	1.91 (1.52–2.41)	< .01
Cannabis	32.1% (3,261)	51.5% (211)	31.2% (3,050)	2.33 (1.91–2.85)	< .01
Cocaine	3.7% (378)	17.6% (72)	3.1% (306)	6.62 (5.01–8.74)	< .01
MDMA (ecstasy)	2.7% (274)	12.8% (52)	2.3% (221)	6.32 (4.60–8.69)	< .01
Amphetamine	2.0% (207)	12.5% (52)	1.6% (155)	8.89 (6.38–12.39)	< .01
GHB / GBL	0.6% (60)	3.2% (13)	0.5% (46)	7.03 (3.79–13.03)	< .01
Ketamine	0.2% (21)	2.4% (10)	0.1% (11)	22.01 (9.31–52.02)	< .01
Caffeine products [b]	92.8% (9,439)	93.2% (383)	92.8% (9,057)	1.07 (0.72–1.58)	.75
Vitamins & OTC drugs [c]	46.0% (4673)	63.4% (260)	45.2% (4413)	2.16 (1.75, 2.67)	< .01
Fictitious drugs [d]	0.2% (25)	1.0% (4)	0.2% (21)	3.51 (1.04, 11.80)	.04

Data are % (number) adjusted for age, gender, and language region. [a] Population-based weights were removed in the regression analyses. [b] Coffee, caffeine tablets, and energy drinks. [c] Herbal sedatives, vitamins, and tonics. [d] Supraval® and Energyl®. PNE: pharmacological neuroenhancement; OTC: over-the-counter.

2.4.4 Multivariate predictors of lifetime PNE

The overall prediction model resulting from a hierarchical logistic regression (R^2 = 0.27) is presented in Table 4 and revealed that the following variables were positively associated with lifetime PNE: being a student, frequent stress in the past 12 months, psychological consulting, lifetime diagnosis of a mental disorder, and lifetime use of cocaine and illegal amphetamine. Having minor children at home and perceived health were negatively associated with lifetime PNE.

Table 4. Odds ratios (OR) for the overall model of the multivariable associations (fully adjusted results) between participant characteristics and lifetime PNE.

	OR (95% CI)	*P*
Sex		
Male	0.78 (0.59, 1.03)	.08
Female		
Age group		
15-24 years		
25-34 years	1.14 (0.69, 1.89)	.60
35-44 years	1.33 (0.77, 2.30)	.31
45-74 years	0.88 (0.52, 1.47)	.62
Professional activity		
In education		
Full-time work ≥ 90%	0.35 (0.21, 0.57)	< .01
Part-time work < 90%	0.39 (0.23, 0.67)	< .01
Monthly income [a]		
< 6,000 CHF		
6,000-10,000 CHF	0.90 (0.66, 1.22)	.50
> 10,000 CHF	1.11 (0.79, 1.57)	.54
Relationship		
None/temporary		
Stable	1.02 (0.77, 1.37)	.87
Children at home < 18		
None		
At least one	0.67 (0.50, 0.91)	.01
Perceived health		
SF-12, scale 1-5	0.76 (0.64, 0.90)	< .01
Stress (12 m)		
SECO, scale 1-5	1.51 (1.31, 1.75)	< .01
Psychological consulting		
Never		
At least once	2.54 (1.90, 3.42)	< .01
Mental disorder [b]		
Never		
At least one	4.26 (3.14, 5.80)	<.01
Lifetime drug use		
Alcohol	0.98 (0.55, 1.75)	.95
Tobacco	1.16 (0.85, 1.58)	.37
Cannabis	1.20 (0.89, 1.61)	.22
Cocaine	2.40 (1.51, 3.82)	< .01
MDMA (ecstasy)	1.48 (0.85, 2.56)	.17
Illegal amphetamine	2.44 (1.37, 4.33)	< .01
Ketamine	2.64 (0.88, 7.87)	.08
GHB/GBL	1.54 (0.58, 4.08)	.39

Population-based weights were removed in the regression analyses. [a] ADD/ADHD, narcolepsy, depression, anxiety disorder, dependency (lifetime diagnosis). SF-12: The 12-Item Short Form Health Survey; SECO: State Secretariat for Economic Affairs. N = 10 084. R^2 = .08 (Cox & Snell), .27 (Nagelkerke). Model χ^2 (22) = 648.846, P < .001.

2.4.5 Prescription drugs used for PNE, motives for use, and source of supply

Tranquilizers and antidepressants were the substances most commonly misused, and current prescription drug misuse within the past 30 days was rare for all prescription drug categories (Table 5). Among PNE users, 26.2% reported lifetime nonmedical use of

tranquillizers, 20.2% antidepressants, 14.2% ADD/ADHD medication, 3.5% beta-blockers, 1.8% modafinil, and 0.4% anti-dementia drugs. The prevalence of nonmedical use of each medication evaluated in the survey is available in the supplementary materials (Table S2). The source of supply for the nonmedical use of prescription drugs was most commonly a doctor (Table 5). However, the main source of supply for ADD/ADHD medication was friends (Table 5). A narrow majority of the PNE users reported the desired effects of PNE with prescription drugs (Table 5).

Table 5. Prevalence of nonmedical prescription drug use for PNE in the study population (N = 10,171), main source of supply, and whether the expectations of use were fulfilled

	LTP	*12-MP*	*30-DP*	*Main source of supply*	*Expectations fulfilled*
Nonmedical prescription drug use					
Tranquilizers	1.06% (108)	0.59% (60)	0.40% (40)	Doctor 53.7% (58)	73.5% (79)
Antidepressants	0.81% (83)	0.37% (38)	0.18% (18)	Doctor 73.8% (61)	70.8% (59)
ADD/ADHD medication	0.57% (58)	0.29% (29)	0.07% (7)	Friend 55.8% (32)	61.0% (35)
Beta-blockers	0.14% (14)	0.04% (4)	0.04% (4)	Doctor 52.8% (8)	72.4% (10)
Modafinil	0.07% (7)	0.04% (4)	0.02% (2)	Friend 31.0% (2)	31.6% (2)
Anti-dementia drugs	0.02% (2)	0	0	Doctor 100.0% (2)	-

Data are % (number) weighted for age, sex, and language region. LTP: lifetime prevalence; 12-MP: 12-month prevalence; 30-DP: 30-days prevalence.

The reported nonmedical use of tranquilizers aimed mainly at improving sleep and relaxation after stress at work or in education (33.5%). The main motive for the nonmedical use of antidepressants was PME at work or for studying (58.8%) but also PME in leisure (38.3%). ADHD medications were most commonly misused for PCE (74.5%). The only two people who mentioned the misuse of an anti-dementia drug both used the drug for the purpose of PCE. The number of participants who used modafinil and beta-blockers without having a prescription was too small to make reliable statements about the motives for use.

2.4.6 Drugs of abuse used for PNE, motives for use, and source of supply

Alcohol users mentioned relaxation during leisure time as their most important motive for drinking alcohol. Partying and getting high were the main motives for the use of illegal drugs (87.4% for MDMA, 77.7% for cocaine, 73.2% for illegal amphetamine, 59.2% for ketamine, 54.7% for cannabis) except for GHB/GBL, for which half of the self-named users reported that their use occurred involuntarily. However, 15.2% of illegal amphetamine and 11.6% of cocaine users reported that they had already used these drugs intentionally for PCE (Table 5). Moreover, the use of alcohol and cannabis to relax and to calm down after stress in the

workplace or education, which would be considered indirect PNE (Maier & Schaub, 2015), was reported by one quarter of alcohol users and one fifth of cannabis users (Table 6).

Table 6. Prevalence of PNE motives (M1-M4) among participants who were experienced with alcohol and illegal drug use for a set of multiple-answer options.

	M1. *PCE (attention, concentration, memory)*	***M2.*** *Reduction of nervousness / stage fright*	***M3.*** *PME at work / for studying*	***M4.*** *Relaxation after stress at work / education*
Lifetime drug use				
Alcohol, *n* = 9,541	0.2% (20)	2.4% (233)	0.6% (60)	25.4% (2,428)
Cannabis, *n* = 3,261	1.0% (33)	2.4% (78)	1.3% (41)	17.4% (568)
Cocaine, *n* = 378	11.6% (44)	2.0% (8)	1.0% (4)	5.7% (22)
MDMA (ecstasy), *n* = 274	3.0% (8)	1.1% (3)	0.3% (1)	6.1% (17)
Amphetamine *n* = 207	15.2% (31)	2.9% (6)	2.1% (4)	4.5% (9)
GHB/GBL, *n* = 60	0	0	0	2.3% (1)
Ketamine, *n* = 21	5.1% (1)	4.3% (1)	5.1% (1)	0

Data are % (number) weighted for age, sex, and language region. PCE: pharmacological cognitive enhancement; PME pharmacological mood enhancement.

The main source of supply for illegal drugs was the circle of friends (91.3% for cannabis, 80.8% for MDMA, 78.7% for illegal amphetamine, 78.0% for cocaine, 69.3% for ketamine, 57.7% for GHB/GBL) and, less commonly, a dealer (41.9% for GHB/GBL, 33.7% for ketamine, 32.9% for MDMA, 29.1% for cocaine, 27.6% for illegal amphetamine, 14.6% for cannabis). Only a minority of users had bought their drugs on the Internet (15.9% for ketamine, 5.9% for GHB/GBL, 2.0% for illegal amphetamine, 0.9% for cocaine, 0.7% for MDMA, 0.5% for cannabis) or received them from family members (9.4% for ketamine, 5.2% for GHB/GBL, 3.0% for cannabis, 2.1% for illegal amphetamine, 2.2% for cocaine, 1.1% for MDMA).

2.5 Discussion

This study is the first representative large-scale study of PNE among the Swiss population that did not focus solely on students but also on employees and surveyed the various substances used for PNE. The study revealed three main findings. 1) Among the study sample, 4.0% reported lifetime use of prescription or recreational drugs for PNE, but only half of these respondents (2.1%) reported PNE within the past year. 2) Lifetime diagnosis of a mental disorder, experience with professional psychological consulting, stress, being a student, living without minor children at home, perceived poor health, and the lifetime use of the illegal stimulants cocaine and amphetamine were the strongest predictors of lifetime PNE. 3) PME was more prevalent than PCE or both PME/PCE.

According to our study, the lifetime and 12-month prevalence rates of PNE were rather low compared to other studies (see Table 1) or general prescription and recreational drug in the Swiss population (Gmel, Kuendig, Notari, & Gmel, 2014; Gmel et al., 2015). This result is consistent with recent research on substance use for PNE among German and Swiss employees (Grebner et al., 2010; Kordt, 2009, 2015) but indicates a lower prevalence compared to Swiss student-only surveys (Maier et al., 2013; Ott & Biller-Andorno, 2014). The willingness to use prescription drugs or recreational drugs for PNE for the hypothetical case that they were effective without any side effects was considerably low among study participants without self-reported PNE (8.7% and 4.0%, respectively). However, the interest in PNE was slightly higher among students, demonstrating the need to monitor PNE among youth in Europe. The authors of a recent study of PNE among UK students claimed that the low prevalence despite high interest might be explained by the lack of availability of prescription drugs (Singh et al., 2014).

Participants who reported a lifetime diagnosis of a mental disorder were more than four times more likely to report PNE. Moreover, participants who felt often or very often stressed during the past 12 months and participants who rated their health as only poor were also more likely to report PNE. Having minor children at home was found to be a protective factor that made the occurrence of PNE unlikely. The association between illegal drug use and PNE established in the literature (Maier et al., 2013; McCabe et al., 2005, 2014; Weyandt et al., 2009) was confirmed in the present study. Participants who reported having used cocaine or illegal amphetamine were more than two times more likely to report PNE.

The nonmedical use of antidepressants and tranquilizers for increased well-being (PME) was more prevalent than stimulant use for cognitive enhancement. Furthermore, the majority of PME users had previously sought help because of a mental health problem and were assumed to misuse their current or past medication for PNE (DeSantis et al., 2008; Gerlach, Dasgupta, Schnoll, & Henningfield, 2014). The finding that the participants reported greater awareness of PCE by others (25.8%) compared to PME by others (19.8%), although opposite prevalence rates of substance use for these purposes were reported, potentially indicating underreporting of PCE in the present study. In addition, the use of sedating substances, such as alcohol and cannabis, to relax after stress in the workplace or education was more common than illicit stimulant use for PCE and can be viewed as a form of indirect PCE if used to increase relaxation to perform better the next day (Maier & Schaub, 2015). The frequent and high use of alcohol (and/or cannabis) as a socially accepted strategy to cope with stress may cause greater harm than occasional PCE with prescription drugs during short periods in life.

However, further studies are needed to determine if PCE use by students continues after graduation.

2.5.1 Strengths, limitations, and implications

A major strength of this study is the large sample of employees and students recruited as part of the Swiss national Internet panel of the LINK institute, which is representative of the Swiss population. Furthermore, thorough weighting procedures were used to investigate substance use for the purpose of cognitive and mood enhancement at work or while studying. Moreover, this survey included authentic photos of each medication to facilitate user recognition and inquired specifically about nonmedical use and its motives. In addition, two fictitious drugs were included to control for socially desirable responding behavior.

However, the ability of the Internet panel to provide representative data may be questioned. Do only middle-class Swiss people with good jobs and a good social context participate in these surveys? Could PNE be underestimated in Switzerland because the stressed population who requires enhancement does not have time to occasionally participate in surveys for an Internet panel? What type of student is likely to engage in an additional Internet panel for surveys if already flooded with invitations to participate in research studies at their higher education institution?

A further limitation is the formulation of the question about PNE. The two main questions asked about participants' use of prescription and recreational drugs to perform better at work or while studying. Most of the participants had most likely not considered indirect enhancement with sedating substances for PNE when responding to questions about substance use for performance. Therefore, a more specific definition of PNE should be implemented in subsequent surveys (Maier & Schaub, 2015). In addition, we asked about a broad range of potential prescription drugs used for PNE (Table S2) but did not address the issue of generic medication.

The identification of two different types of PNE users with different motives for substance use has several implications for preventing physical and mental harm. First, healthy PNE users without a current or past mental disorder should be informed about the possible risks and side effects of PNE use. Academic institutions and companies could provide students and employees with information about strategies other than substance use and develop stress-management training as tools for early prevention of PNE in healthy individuals. Moreover, increased communication about the addiction potential of certain drugs used for PNE is needed, and doctors should be able to furnish objective information about the effects, side effects, and individual differences in response to prescription drugs. Second, PNE users with

an underlying mental disorder who receive no or only insufficient treatment should be informed about further treatment options. Corporate interventions must be implemented if the mental disorder is associated with the workplace situation and job changeover is not desired. Third, workplace health promotion should address the issue of stress and successful coping strategies before PNE occurs. This goal could be achieved by strengthening the social and communication skills of the employees and management. Finally, future research should investigate differences between PNE users with and without a current or past mental disorder. The motives and profiles of "healthy" and more vulnerable PNE users likely differ and consequently require different intervention measures.

2.6 Conclusions

Our research constitutes the first comprehensive and representative large-scale study of PNE on a national level in Europe. Among the Swiss population, 4.0% reported lifetime PNE, but only 2.1% reported past-year PNE. Lifetime PNE was strongly associated with prior diagnosis of at least one mental disorder, with being a student rather than employed, and with illegal stimulant use experience. PNE is not (yet) common among the Swiss population, but monitoring further development is recommended.

Acknowledgments

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Conflicts of interest

The authors have no financial disclosures and no competitive interests. The study funders (SUVA) did not influence the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

2.7 Supplementary Material

Methods S1 Specification of the questionnaire design. To include all relevant issues, question items were taken from existing European questionnaires about (workplace) stress or about substance use for cognitive enhancement (BFS, 2013; Eurofound, 2010; Grebner et al., 2010; Kordt, 2009; Middendorff et al., 2012). Questions about frequency and patterns of psychoactive substance use were formulated consistent with the Addiction Monitoring in Switzerland criteria (Gmel, Kündig, Notari, Gmel, & Flury, 2013). The questionnaire included questions on socio-demographic data, stress at work or in education (Eurofound, 2010; Grebner et al., 2010; Semmer, Zapf, & Dunckel, 1999), health (BFS, 2013), and substance use (Gmel et al., 2013; Middendorff et al., 2012).

The substance use section considered both the use of alcohol and illegal drugs (cannabis, cocaine, MDMA, amphetamines, ketamine, and GHB/GBL) in the study population and the nonmedical use of prescription drugs among PNE users. Together with an addiction medicine specialist, we examined which medications were potentially used for PNE and evaluated them in the survey. For each prescription drug category, respondents had to indicate the frequency of use within the past 30 days, motives for use, and whether their expectations regarding the medication's effects were met. These questions were asked for the nonmedical use of the following groups of substances: methylphenidate, modafinil, activating antidepressants including selective serotonin reuptake inhibitors (SSRI), anti-dementia agents, tranquilizers, and beta-blockers. Moreover, all prescription drugs of each category were presented graphically with packaging and pills to facilitate recognition by the survey participants (Novak et al., 2007). Additionally, all participants had to answer questions about their use of freely available "soft" enhancing substances such as tobacco, coffee, caffeine tablets, energy drinks, herbal sedatives (e.g., St. John's Wort, common valerian), and vitamins and tonics (e.g., gingko biloba, zinc). For the use of each substance, eight motives were suggested to the users randomly: three motives related to direct enhancement at work or in education (to enhance cognition, to enhance mood, and to reduce nervousness), one motive related to indirect enhancement at work or in education (to relax after stress at work), and four other motives for nonmedical use (to get high, enhance mood in leisure time, relax in leisure time, work despite pain). Additional general motives for use, such as pleasure or taste (e.g., for alcohol), could be mentioned by the participants.

To control for socially desirable responding, an additional category of "energy boosters" with two fake medications (Supraval®, Energyl®) was included (Novak et al., 2007). Moreover, the survey contained questions on the past and current diagnosis of mental

disorders (ADHD, narcolepsy, depression, anxiety disorder, and substance dependence) that are known to be treated with medications often referred to as PNE drugs in scientific literature (Farah et al., 2014; Rabiner et al., 2009a).

Table S1. Percentage quota, number of interviews realized (absolute & percentage), and the resulting weighting factor for data from the different linguistic regions of Switzerland

	Quota (%)	Realized interviews (*n*)	Realized interviews (%)	Difference	Weighting factor
German-speaking					
Male, 15-24 years	5.64	567	4.16	1.48	1.36
Male, 25-34 years	6.39	802	5.89	0.50	1.09
Male, 35-44 years	6.97	919	6.75	0.22	1.03
Male, 45-54 years	7.43	1,114	8.18	-0.75	0.91
Male, 55-64 years	5.62	861	6.32	-0.70	0.89
Male, 65-74 years	4.05	517	3.80	0.26	1.07
Female, 15-24 years	5.42	676	4.96	0.46	1.09
Female, 25-34 years	6.28	810	5.95	0.33	1.06
Female, 35-44 years	6.91	971	7.13	-0.22	0.97
Female, 45-54 years	7.25	1,077	7.91	-0.66	0.92
Female, 55-64 years	5.66	865	6.35	-0.69	0.89
Female, 65-74 years	4.49	688	5.05	-0.57	0.89
French-speaking					
Male, 15-24 years	1.84	154	1.13	0.71	1.63
Male, 25-34 years	2.07	300	2.20	-0.13	0.94
Male, 35-44 years	2.26	347	2.55	-0.29	0.89
Male, 45-54 years	2.41	323	2.37	0.04	1.02
Male, 55-64 years	1.82	271	1.99	-0.17	0.92
Male, 65-74 years	1.31	186	1.37	-0.06	0.96
Female, 15-24 years	1.77	255	1.87	-0.10	0.95
Female, 25-34 years	2.04	265	1.95	0.10	1.05
Female, 35-44 years	2.25	294	2.16	0.09	1.04
Female, 45-54 years	2.35	289	2.12	0.23	1.11
Female, 55-64 years	1.84	235	1.73	0.12	1.07
Female, 65-74 years	1.45	196	1.44	0.01	1.01
Italian-speaking					
Male, 15-24 years	0.31	44	0.32	-0.01	0.96
Male, 25-34 years	0.33	51	0.37	-0.04	0.88
Male, 35-44 years	0.44	60	0.44	0.00	1.00
Male, 45-54 years	0.47	71	0.52	-0.05	0.90
Male, 55-64 years	0.36	56	0.41	-0.05	0.88
Male, 65-74 years	0.32	43	0.32	0.01	1.01
Female, 15-24 years	0.30	42	0.31	-0.01	0.97
Female, 25-34 years	0.33	46	0.34	-0.01	0.98
Female, 35-44 years	0.45	66	0.48	-0.04	0.93
Female, 45-54 years	0.46	67	0.49	-0.03	0.94
Female, 55-64 years	0.37	51	0.37	-0.01	0.99
Female, 65-74 years	0.34	40	0.29	0.04	1.16

Table S2. Lifetime prevalence of the nonmedical prescription drug use for pharmacological neuroenhancement and the use of freely available "soft" enhancers for increased performance at work or for studying among the study sample (N = 10,171)

Nonmedical prescription drug use for increased performance at work or for studying	
Tranquilizers	**1.06% (108)**
Temesta®	0.38% (39)
Stilnox®	0.33% (34)
Xanax®	0.27% (28)
Seresta®	0.22% (23)
Valium®	0.19% (20)
Dormicum®	0.17% (17)
Remeron®	0.09% (9)
Imovane®	0.07% (7)
Halcion®	0.03% (3)
Dalmadorm®	0.02% (2)
Noctamid®	0
Antidepressants	**0.81% (83)**
Cipralex®	0.43% (43)
Seropram®	0.18% (19)
Cymbalta®	0.16% (17)
Fluctine®	0.13% (14)
Efexor®	0.13% (13)
Zoloft®	0.10% (11)
Wellbutrin®	0.05% (5)
Erdonax®	0.03% (3)
ADHD medication	**0.57% (58)**
Ritalin®	0.48% (49)
Concerta®	0.12% (12)
Medikinet®	0.05% (5)
Focalin®	0.05% (4)
Strattera®	0.01% (1)
Beta-blockers	**0.14% (14)**
Beloc ZOK®	0.08% (8)
Meto Zerok®	0.07% (7)
Modafinil (Modasomil®)	**0.07% (7)**
Anti-dementia drugs	**0.02% (2)**
Aricept®	0.02% (2)
Axura®	0
Exelon®	0
Reminyl®	0

Use of freely available "soft" enhancers for increased performance at work or for studying	
Herbal sedatives	**18.8% (1,917)**
Zeller-Entspannung®	11.2% (1,137)
Baldriparan®	7.5% (765)
Jarsin®	2.0% (203)
Zeller Herz-Nerven®	1.4% (139)
Remotiv®	1.3% (131)
Faros®	0.2% (16)
Vitamins and tonics	**38.4% (3,910)**
Berocca®	18.1% (1,838)
Supradyn®	16.5% (1,675)
Strath®	11.7% (1,192)
Dynamiasan®	7.2% (731)
Tonoglutal®	2.6% (263)
Gincosan®	1.2% (125)
Caffeine	**92.8% (9,439)**
Coffee	87.8% (8,929)
Caffeine tablets	1.8% (183)
Energy Drinks	47.5% (4,833)
Nicotine (tobacco)	**63.2% (6,424)**

Data are % (number) weighted for age, sex, and language region.

3 The Importance of Stress, Self-Efficacy, and Self-Medication for Pharmacological Neuroenhancement among Employees and Students

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Author contributions

MPS and LJM designed the study based on the findings of their previous feasibility study on pharmacological neuroenhancement in Switzerland. LJM took photographs of all prescription drugs and over-the-counter drugs which were presented to the participants together with the survey questions. MPS and LJM collaborated with the LINK institute to implement, pilot, and validate the online survey, and to collect the data. The LINK institute provided some preliminary descriptive results. LJM analyzed and interpreted the data, and drafted the manuscript. MPS and SH reviewed the manuscript and provided methodological suggestions, and LJM revised the manuscript accordingly.

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3.1 Abstract

Objectives: This study examined the relationship between stress, self-efficacy, self-medication, and pharmacological neuroenhancement (PNE) in the Swiss general population. **Methods:** Using the largest Swiss Internet panel, a sample of 10,171 employees and students (unweighted *N* = 10,084) aged 15 to 74 years was recruited and asked to complete a self-administered online survey. The data were weighted for age, sex, and language region to provide results that were representative of the Swiss population. Multinomial logistic regression models were conducted to identify predictors of pharmacological cognitive enhancement (PCE) and pharmacological mood enhancement (PME) over the past year. Two self-medication models and an overall model were determined. **Results:** Current medical treatment for a mental disorder was the best predictor of both PCE and PME use as serious self-medication. The overall model revealed that cannabis use, frequent stress, and long-term stress were predictors of both PCE and PME, whereas negative stressors and time pressure at work did not remain in the final model. Furthermore, past-year PCE with and without PME was associated with being male, being a student, and using illegal drugs other than cannabis, whereas being female and having low self-efficacy predicted past-year PME only. **Conclusions:** Consideration of the predictor variables identified in this study may help to identify the potential PCE and PME users for whom measures to prevent drug abuse and manage stress are most appropriate. More specifically, the use of PCE and PME as self-medication to enhance performance at work or while studying needs further consideration in the neuroenhancement debate.

Keywords: Neuroenhancement, cognitive enhancement, mood enhancement, self-medication, illegal drug use, mental health

3.2 Introduction

Pharmacological neuroenhancement (PNE) refers to the nonmedical use of prescription drugs, alcohol, and illegal drugs for the purpose of enhancing cognition, mood, or pro-social behavior to improve performance at work or while studying (de Jongh et al., 2008; Maier and Schaub, 2015). Nonmedical use of prescription drugs is defined as use without having a prescription or use for another purpose than prescribed (Maier and Schaub, 2015). More specifically, some people with a mental disorder use their medication in higher doses or through a different route of administration than prescribed for the purpose of enhanced cognitive performance (Arria et al., 2008; Maier et al., 2013).

However, the literature most likely focuses on healthy individuals' nonmedical use of prescription stimulants for pharmacological cognitive enhancement (PCE). For the most part, the discussions are limited to the question whether the drugs used for PCE affect the cognitive processes in users without considering altered emotion sufficiently (Vrecko, 2013). Nevertheless, stimulants' effects are not purely cognitive, but also affective and the motivational effects are significantly involved in performance outcomes (Ilieva and Farah, 2013; Vrecko, 2013). Stimulants' effect on enhanced motivation might also explain why healthy users still perceived an enhanced cognitive function, when no objective cognitive enhancing effects were found (Ilieva et al., 2013).Furthermore, potential motivational enhancing drug effects are also relevant when considering pharmacological mood enhancement (PME) or substance use to cope with stress (de Jongh et al., 2008; Maier and Schaub, 2015).

However, an increasing number of media reports on PNE might generate the misperception that PNE is an acceptable means of coping with stress and overwhelming demands at work or school (Schleim, 2014; Wolff and Brand, 2013). Lazarus described stress as a feeling that arises when professional or academic requirements exceed the personal and social resources that an individual is able to mobilize at a given time (Lazarus, 1989). A comprehensive study among German students supported this theory and found an association between performance pressure and PNE (Middendorff et al., 2012). A further interesting study finding was that one quarter of students experienced with PNE reported cannabis use to cope with the study demands (Middendorff et al., 2012).

Notwithstanding, responses to stress can vary greatly among individuals; the use of prescription and recreational drugs for PNE represents only one of many possible pharmacological coping strategies (Maier and Schaub, 2015; Park and Iacocca, 2014). Moreover, PNE with stimulants is strongly associated with risky health behaviors such as

illegal drug use (Arria et al., 2008; McCabe et al., 2005). Insufficient coping skills and substance abuse in the face of chronic stress might cause mental health problems, and vice versa (Mohr et al., 2014). Additionally, individual and situation-specific differences in the perception of stress and in coping strategies are related to decisions about whether to engage in PNE (Sattler et al., 2014).

Self-efficacy is the ability to initiate and use successful stress coping strategies (Bandura, 1977) and mediates the path from stress to illness (Sawatzky et al., 2012). In addition, a study found that students with high achievement goals and high self-efficacy performed better than their counterparts (Cheng and Chiou, 2010). These findings refer to Bandura's (1986) social cognitive theory, which states that attainable goals, self-motivation, and controllable outcomes are crucial for self-efficacy and personal development. Once the individuals in these studies experienced PNE, they showed lower levels of avoidance self-efficacy because they could no longer avoid using illicit stimulants in highly stressful situations (Bavarian et al., 2013). In other words, they were not confident in their own abilities and the functional use of drugs for enhancement purposes even further diminished self-efficacy when performance was attributed to the drug effects rather than to one’s own abilities.

Responsible self-medication with indicated over-the-counter drugs for self-recognized conditions is an important element of self-care that reduces the burden on health care systems (WHO, 1998). However, Khantzians' (1997) self-medication hypothesis of addictive disorders claims that addicts use alcohol or illegal drugs to change the painful affect states that can result in addiction. The nonmedical use of prescription drugs or alcohol and illegal drugs for PCE or PME to treat an undesired physical or mental condition represents a form of *self-medication* that falls in the middle of the range between healthy self-care and addiction. However, the terms nonmedical use or misuse are preferred in the scientific literature, and definitions that contain the term “enhancement” arise from the bioethical debate (Racine and Forlini, 2008). These technical and optimistic terms increase good performers’ fear of inadequacy and distract from the issue of *serious self-medication* among individuals with a mental disorder who use drugs to diminish certain higher-order capacities that cause specific symptoms of a disorder (Earp et al., 2014). An example provided by Earpand colleagues (2014) is the diminishment of memory to reduce traumatic memories. Another example might be diminishment of a certain brain function to reduce rumination in patients suffering from depression. Consequently, it often remains unclear whether drug use for cognitive enhancement in individuals with an undiagnosed mental disorder, such as ADHD, is self-treatment or misuse (Peterkin et al., 2011; Rabiner et al., 2009a). Both PCE and PME might

be considered *self-medication* when healthy individuals use drugs to maintain good performance when few resources are available or to improve performance from good to excellent or from pathological to normal. Thus, PCE and PME are means of achieving specific health or performance goals (Wolff et al., 2014). For the most part, studies of academic PCE have focused on PCE as *moderate self-medication* in terms of the self-optimization of healthy individuals who suffer from stress (Singh et al., 2014; Wolff and Brand, 2013). Research has often excluded individuals with mental disorders to avoid the discussion of where treatment ends and enhancement begins (Barrett et al., 2008; Maslen et al., 2014). The use of PCE and PME as *serious self-medication* to combat symptoms of mental disorders or the adverse side effects of medical treatment is prevalent (Kasten, 1999) but has not yet been investigated in the neuroenhancement literature. Therefore, the current study aimed to investigate factors associated with the use of both *moderate self-medication* and *serious self-medication* to enhance performance at work or while studying.

3.2.1 Current study

The current study is the first to perform an in-depth analysis of the predictors of two different forms of neuroenhancement, namely PCE and PME, based on representative national-level estimates. Mental disorders and their associated medical treatments as well as different forms of stress and self-efficacy were considered as possible predictors of PCE and PME. Taking into account the abovementioned theoretical work, stress and insufficient stress coping, other illegal drug use, and impaired mental health were assumed to predict both PCE and PME. Moreover, it was assumed that different enhancement intentions are related to different predictors. PME with the intention to increase psychological well-being differs from the rather competitive intention of PCE (Maier and Schaub, 2015; Schleim, 2014). Finally, the following hypotheses were made in terms of a *moderate self-medication*:

- past-year PCE and PME are both associated with higher levels of past-year stress and long-term stress
- past-year PCE is associated with time pressure and other negative professional or academic stressors in the past year
- past-year PCE and PME are both associated with illegal drug use in the past year
- past-year PME is associated with low self-efficacy

In addition, the following *serious self-medication* hypothesis was made:

- past-year PCE and PME are both associated with current medical treatment for underlying mental disorders

The understanding of the predictors of PCE and PME derived from this cross-sectional study has important implications for preventive measures and future longitudinal research that aims to disentangle the relationships among stress, self-efficacy, mental health, and PCE and PME.

3.3 Methods

3.3.1 Enrollment procedure and study sample

Participants were recruited through a national Internet panel. The Internet panel of the LINK institute for market and social research in Switzerland includes more than 130,000 people living in Switzerland who consented to be contacted about online public opinion surveys during computer-assisted telephone interviews. The panelists were representative of the 15- to 74-year-old population in Switzerland that uses the Internet at least once per week for private purposes and is able to answer a questionnaire in German, French, or Italian. In March 2013, the LINK institute invited 39,996 panelists to participate in a study about health and stress at work and in education, and 18,094 panelists took the survey. Following screening for exclusion criteria (currently unemployed and not in education = 3,535), quota overflow (n = 2,155), and dropouts (n = 2,320), the final sample size was 10,084. The data were weighted for age, sex and language region (weighted N = 10,171). Informed consent was obtained from all of the participants who were included in the study.

3.3.2 Measures

A self-administered online survey was used to investigate PCE and PME in Switzerland (for survey details see Maier et al., in press). For the present study, only variables containing current and past-year indicators of stress, health, and health behaviors were considered.

3.3.3 Outcome variable

Pharmacological neuroenhancement (PNE). Two principal questions assessed past-year PNE. First, participants who indicated having ever used prescription drugs or recreational drugs for cognitive enhancement (PCE) at work or while studying were asked, whether use also occurred in the past 12 months. Second, participants who indicated having ever used prescription drugs or recreational drugs for mood enhancement (PME) at work or while studying were asked whether use also occurred in the past 12 months. The following four

groups were specified: 1) no PNE in the past 12 months; 2) past-year PME only; 3) past-year PCE; and 4) both past-year PME and PCE. To provide sufficient statistical power for logistic regression analyses performed, groups 3 and 4 were merged to one group containing all PCE users with and without additional PCE use.

3.3.4 Stress measures

Frequency of stress. To determine the participants' frequency of stress experiences in the past 12 months, they were asked the following question: "During the past 12 months, how often have you felt stressed – never, rarely, sometimes, often, or very often?" This variable was modeled using the original Likert format.

Long-term stress at work or in education. To determine whether the participants had experienced long-term stress at work or in education, they were asked the following question: "Have you experienced stress at work or in education that persisted over several months? (Eurofound, 2010)" The answer format was dichotomous (yes or no).

Time pressure and negative aspects at work or in education. The participants answered seven questions about current stress at work or in education that were analyzed by an exploratory factor analysis. The factor analysis revealed two stress scales, which were used as potential predictors of PCE and PME. The first scale included two items ($\alpha = .76$) asking for frequency of working or learning at a fast pace and under tight deadlines (Eurofound, 2010; Grebner et al., 2010). The items were answered on a 6-point scale (almost never, approximately one-quarter of the time, approximately half of the time, approximately three-quarters of the time, almost always, and always). The second stress scale included five items ($\alpha = .67$) that measured time-independent negative conditions of the participants' current work and education situations that might be related to adverse health outcomes and PNE. Those items asked about the frequency of unclear instructions from supervisors and lecturers, the occurrence of unnecessary breaks at work or while studying, the feeling of a lack of control at work or while studying, competitive pressure, and the need to show inauthentic feelings at work or at school (Eurofound, 2010; Grebner et al., 2010). Each of the five items was coded on a 5-point scale (never, rarely, sometimes, often, or very often).

3.3.5 Other predictor variables

Socio-demographic characteristics. The following demographic variables were included in the analyses: sex, age (15-24, 25-34, 35-44, 45-54, and 55-74 years), professional activity (student, employed full-time, and employed part-time), relationship (none/temporary and stable), and the presence of children (< 18 years of age) at home (yes or no).

Mental health and health behavior. The participants indicated their current health status in response to the first question of the 12-Item Short Form Health Survey SF-12 (poor, fair, good, very good, and excellent), a survey often used by physicians determine patients' health. Moreover, participants were asked about past and current diagnoses of mental health disorders (ADHD, narcolepsy, depression, anxiety disorder, and substance use disorder) that are known to be treated with medications that the scientific literature often refers to as neuroenhancement drugs (Rabiner et al., 2009b; Sattler et al., 2014). A dichotomous variable was used in the analysis to represent the current use of a prescription drug to treat at least one of the aforementioned mental disorders (yes or no). Participants who reported undergoing medical treatment for a past or current mental disorder were asked whether they had ever used their prescribed medication in a manner other than prescribed (e.g., at a higher dose or via a different route of administration). Past-year psychoactive substance use was assessed dichotomously for tobacco, alcohol, cannabis, and other illegal drugs (cocaine, MDMA, amphetamine, ketamine, and GHB/GBL).

Self-efficacy. The Generalized Self-Efficacy Scale (GSES) was used to assess the strength of the participants' belief in their ability to respond to novel or difficult situations and to cope with a variety of stressors (not at all true, barely true, moderately true, and very true). The psychometric characteristics of the GSES are satisfactory when implemented online (Schwarzer et al., 1999), and the present study revealed good internal consistency ($\alpha = .86$).

3.3.6 Logistic Regression Models

To evaluate each variable's ability to predict the outcome (PME or PCE with and without PME), initial separate multinomial logistic regression analyses were performed (subsequently termed 'univariate analyses'). Past-year non-users were the reference group for the dependent variable. First, all significant univariate socio-demographic predictors were entered in the preliminary multivariate model (model 1). Non-significant variables were removed from the overall model one at a time. Nagelkerke's R-square was calculated as a goodness-of-fit measure for the multivariate multinomial logistic regression model. In a second model, the demographics, stress, and self-efficacy were entered as predictors of PME and PCE with and without PME (*moderate self-medication*, model 2). In model 3 (*serious self-medication*), the demographics and current medical treatment for a mental disorder were entered. Finally, in an overall multivariate multinomial logistic regression model all remaining significant predictors were included to predict PME and PCE with and without PME (model 4). All quantitative analyses were conducted using IBM SPSS Statistics Version 22 (SPSS, Inc., Chicago, IL, USA), and $p < .05$ was set as the significance level.

3.4 Results

Of the study participants, 2.1% (*n* = 215) reported past-year PNE. Two-thirds of the past-year PNE users (69.2%) felt frequently or very frequently stressed in the past 12 months, compared with 35.5% of the non-users. Four out of five past-year PNE users (80.7%) reported long-term stress at work or in education, whereas half of the non-users (49.3%) reported such long-term stress. Whereas the non-users who said they experienced long-term stress reported that they were rarely unable to cope with their stress (7.6%), one-quarter of the PNE users (22.9%) were never or almost never able to cope with stress at work or in education. To further specify the groups of interest, 1.4% (*n* = 146) reported past-year PME and 0.7% (*n* = 69) reported past-year PCE with or without PME.

The characteristics of the study sample used in the analysis of the two different types of past-year PNE are depicted in Table 7. All variables except past-year alcohol use were univariate predictors of either past-year PME or past-year PCE with and without PME (Table 7).

Table 7. Characteristics of the study population with and without current PNE (12 months) and the univariate multinomial associations of each variable with PME and PCE (reference group: no PNE during the past 12 months [no current PNE])

	No current PNE	*PME, 12 months*		*PCE, 12 months*	
	n = 9,956	*n* = 146	*OR (95%CI)*	*n* = 69	*OR (95%CI)*
Sex					
Male (Ref.)	98.2% (5,335)	1.0% (56)		0.8% (42)	
Female	97.5% (4,621)	1.9% (90)	1.86 (1.33-2.60)**	0.6% (27)	0.74 (0.46-1.21)
Age in years					
15-24 (Ref.)	96.7% (1,814)	1.8% (33)		1.6% (30)	
25-34	98.1% (2,104)	1.2% (25)	0.66 (0.39-1.12)	0.7% (15)	0.42 (0.23-0.79)**
35-44	98.0% (2,206)	1.6% (37)	0.92 (0.57-1.47)	0.4% (8)	0.22 (0.10-0.48)**
45-54	98.2% (2,377)	1.4% (34)	0.79 (0.49-1.28)	0.4% (9)	0.24 (0.12-0.50)**
55-74	98.4% (1,454)	1.1% (17)	0.64 (0.35-1.15)	0.5% (7)	0.30 (0.13-0.68)**
Professional activity					
Student (Ref.)	96.1% (1,321)	1.8% (25)		2.1% (28)	
Full-time work ≥ 90%	98.4% (5,456)	1.2% (67)	0.64 (0.41-1.02)	0.4% (21)	0.18 (0.10-0.31)**
Part-time work < 90%	97.7% (3,169)	1.7% (54)	0.90 (0.56-1.45)	0.6% (19)	0.28 (0.16-0.50)**
Relationship					
None / temporary (Ref.)	97.0% (2,703)	2.2% (62)		0.8% (23)	
Stable	98.2% (7,252)	1.1% (85)	0.51 (0.37-0.71)**	0.6% (46)	0.75 (0.46-1.25)
Children in the household					
None (Ref.)	97.5% (6,371)	1.6% (105)		0.9% (58)	
At least one <18	98.6% (3,585)	1.1% (41)	0.69 (0.48-1.00)*	0.3% (11)	0.32 (0.17-0.62)**

years old					
Drug use past 12 months					
No tobacco (Ref.)	98.4% (6,799)	1.1% (78)		0.4% (30)	
Tobacco	96.7% (3,157)	2.1% (68)	1.89 (1.36-2.62)**	1.2% (39)	2.77 (1.71-4.47)**
No alcohol (Ref.)	97.7% (966)	1.4% (13)		0.9% (9)	
Alcohol	97.9% (8,990)	1.4% (133)	1.07 (0.61-1.88)	0.6% (59)	0.69 (0.34-1.38)
No cannabis (Ref.)	98.3% (9,248)	1.2% (114)		0.5% (47)	
Cannabis	92.9% (708)	4.2% (32)	3.68 (2.47-5.48)**	2.9% (22)	6.12 (3.66-10.21)**
No other illegal drugs (Ref.)	98.0% (9,848)	1.4% (142)		0.5% (54)	
Other illegal drugs [a]	85.1% (108)	3.3% (4)	2.69 (1.00-7.25)**	11.6% (15)	24.84 (13.53-45.60)**
Stress					
Not long-term (Ref.)	99.2% (5,049)	0.5% (26)		0.3% (16)	
Long-term	96.6% (4,907)	2.4% (120)	4.81 (3.14-7.37)**	1.0% (53)	3.45 (1.97-6.06)**
Frequency 12 months scale 1-5	3.2 (0.9)	4.1 (0.9)	2.89 (2.38-3.51)**	3.9 (1.0)	2.12 (1.63-2.76)**
Time pressure scale 1-6	3.2 (1.2)	3.6 (1.2)	1.30 (1.14-1.48)**	3.5 (1.2)	1.21 (1.00-1.46)*
Negative aspects scale 1-5	2.4 (0.6)	2.7 (0.7)	2.16 (1.70-2.73)**	2.6 (0.7)	1.90 (1.34-2.69)**
Self-efficacy scale 10-40	30.0 (4.1)	27.0 (0.7)	0.86 (0.83-0.89)**	28.1 (5.9)	0.90 (0.86-0.95)**
Perceived health scale 1-5	3.5 (0.8)	2.8 (0.9)	0.33 (0.27-0.41)**	3.0 (0.9)	0.45 (0.33-0.61)**
Current medical treatment for a mental disorder [b]					
No	98.9% (9,665)	0.7% (65)		0.4% (39)	
Yes	72.4% (291)	20.3% (81)	41.71 (29.49-58.99)**	7.4% (30)	25.06 (15.33-40.96)**

Note. Data are % (n) or mean (*SD*). PCE = pharmacological cognitive enhancement; PME = pharmacological mood enhancement; PNE = pharmacological neuroenhancement.

[a] Cocaine, ecstasy (MDMA), amphetamines (speed), ketamine, GHB/GBL
[b] ADHD, narcolepsy, depression, anxiety disorder, dependency

* $p < 0.05$; ** $p < 0.01$

Results from models 1 – 3 are depicted in Table 8. The demographic predictors (model 1) explained 14% of the variance (Nagelkerke's R^2). The *moderate self-medication* model, which included demographics, stress, and self-efficacy (model 2) explained 19% of the variance. Frequent stress in the past 12 months and long-term stress at work or in education were good predictors of PCE and PME, but time pressure at work and negative stressors at work were excluded from the model. Self-efficacy predicted past-year PME. Finally, the *serious self-medication* model which included both the demographic predictors and current medical treatment for a mental health problem (model 3) explained 30%.

Table 8. Multiple prediction models for PME and PCE with and without PCE in the past 12 months (reference group: no PME/PCE in the past 12 months)

	PME only, 12 months *n* = 146, *OR (95%CI)*	PCE with and without PME, 12months *n* = 69, *OR (95%CI)*
Model 1 (socio-demographic data)		
Sex		
Male (Ref.)		
Female	1.69 (1.17-2.45)**	0.52 (0.30-0.89)*
Professional activity		
Student (Ref.)		
Full-time work ≥ 90%	1.15 (0.67-1.97)	0.37 (0.19-0.71)**
Part-time work < 90%	0.99 (0.59-1.64)	0.14 (0.07-0.27)**
Relationship		
None/temporary (Ref.)		
Stable	0.61 (0.42-0.87)**	1.99 (1.12-3.54)*
Children in the household		
None (Ref.)		
At least one <18 years old	0.91 (0.61-1.34)	0.41 (0.20-0.83)*
Drug use past 12 months		
No cannabis (Ref.)		
Cannabis	3.54 (2.28-5.49)**	1.94 (1.02-3.70)*
No other illegal drugs (Ref.)		
Other illegal drugs [a]	1.14 (0.40-3.24)	15.47 (7.26-33.00)**
Perceived health scale 1-5	0.34 (0.28-0.43)**	0.42 (0.31-0.58)**
Model 2 (*moderate self-medication*)		
Socio-demographic data (model 1)		
Stress		
Not long-term (Ref.)		
Long-term	2.00 (1.24-3.19)**	1.98 (1.04-3.76)*
Frequency 12 months, scale 1-5	1.81 (1.45-2.27)**	1.54 (1.13-2.11)**
Self-efficacy, scale 10-40	0.92 (0.88-0.95)**	0.96 (0.90-1.02)
Model 3 (*serious self-medication*)		
Socio-demographic data (model 1)		
Current medical treatment for a mental disorder [b]		
No		
Yes	32.77 (22.20-48.38)**	24.91 (13.76-45.09)**

Note. N = 10,171. Model 1: R^2 = .03 (Cox & Snell), .14 (Nagelkerke). Model χ^2 (16) = 296.898, $p < .001$; Model.2: R^2 = .04 (Cox & Snell), .19 (Nagelkerke). Model χ^2 (22) = 409.561, $p < .001$; Model 3: R^2 = .06 (Cox & Snell), .30 (Nagelkerke). Model χ^2 (18) = 656.208, $p < .001$; PCE = pharmacological cognitive enhancement; PME = pharmacological mood enhancement.

[a] Cocaine, ecstasy (MDMA), amphetamines (speed), ketamine, GHB/GBL
[b] ADHD, narcolepsy, depression, anxiety disorder, dependency

* $p < 0.05$; ** $p < 0.01$

The overall prediction model resulting from the multinomial logistic regression (R^2 = .33) is presented in Table 9. Current medical treatment was the strongest predictor of both PME

and PCE with and without PME. Past-year cannabis use and frequent and long-term stress were also predictors of both PME and PCE with and without PME. The past-year use of other illegal drugs, being male, being a student, being in a relationship, and living without minor children at home were predictors of PCE with and without PME. Being female and having low self-efficacy were predictors of PME only.

Table 9. Overall multiple prediction model with and without PME in the past 12 months (reference group: no PME/PCE in the past 12 months)

	PME only, 12 months n = 146, OR (95%CI)	*PCE with and without PME, 12 months n = 69, OR (95%CI)*
Sex		
Male (Ref.)		
Female	1.58 (1.06-2.36)*	0.51 (0.29-0.89)*
Professional activity		
Student (Ref.)		
Full-time work ≥ 90%	1.17 (0.68-2.01)	0.16 (0.08-0.32)**
Part-time work < 90%	0.95 (0.53-1.71)	0.28 (0.13-0.57)**
Relationship		
None/temporary (Ref.)		
Stable	0.71 (0.47-1.05)	2.30 (1.26-4.17)**
Children in the household		
None (Ref.)		
At least one <18 years old	0.89 (0.58-1.36)	0.38 (0.19-0.78)**
Drug use 12 months		
No cannabis (Ref.)		
Cannabis	4.73 (2.89-7.23)**	2.86 (1.48-5.52)**
No other illegal drugs (Ref.)		
Other illegal drugs [a]	1.01 (0.33-3.12)	11.99 (5.48-26.22)**
Stress		
Not long-term (Ref.)		
Long-term	2.03 (1.24-3.31)**	2.12 (1.10-4.07)*
Frequency 12 months, scale 1-5	1.61 (1.28-2.02)**	1.43 (1.06-1.94)*
Self-efficacy, scale 10-40	0.93 (0.90-0.97)**	0.98 (0.93-1.04)
Current medical treatment for a mental disorder [b]		
No		
Yes	27.64 (18.78-40.68)**	23.17 (12.91-41.58)**

Note. N = 10,171. R^2 = .07 (Cox & Snell), .33 (Nagelkerke). Model χ^2 (22) = 708.669, $p < .001$; PCE = pharmacological cognitive enhancement; PME = pharmacological mood enhancement; PNE = pharmacological neuroenhancement.

[a] Cocaine, ecstasy (MDMA), amphetamines (speed), ketamine, GHB/GBL
[b] ADHD, narcolepsy, depression, anxiety disorder, dependency

* $p < 0.05$; ** $p < 0.01$

Table 10 presents the prevalence mental disorders according to self-report data of non-users, PME users, and PCE users with and without PME. The majority of the PME users

reported being diagnosed with depression, and half of them reported undergoing current medical treatment for their disorder. Only a small number of the participants with a mental disorder reported that they had ever misused their medication for a purpose other than that for which it was prescribed.

Table 10. Lifetime prevalence of specified mental disorders and associated medical treatment and medication misuse across study groups

	No current PNE *n* = 9,956	PME only, 12 months *n* = 146	PCE with and without PME, 12 months *n* = 69
Depression			
Lifetime diagnosis	12.0% (1,194)	72.2% (106)	55.1% (38)
Received medical treatment	8.0% (796)	70.4% (103)	44.4% (31)
Current medical treatment	2.2% (221)	51.9% (76)	29.6% (20)
Ever misused	0.3% (33)	6.2% (9)	10.9% (7)
ADHD			
Lifetime diagnosis	1.7% (174)	6.0% (9)	28.6% (20)
Received medical treatment	0.6% (62)	2.6% (4)	19.1% (13)
Current medical treatment	0.2% (22)	0	15.9% (11)
Ever misused	0.1% (7)	0.9% (1)	4.4% (3)
Anxiety disorder			
Lifetime diagnosis	8.3% (822)	42.7% (62)	24.4% (17)
Received medical treatment	3.4% (338)	31.8% (46)	9.7% (7)
Current medical treatment	0.8% (82)	20.7% (30)	6.9% (5)
Ever misused	0.2% (17)	5.3% (8)	2.9% (2)
Substance use disorder			
Lifetime diagnosis	3.7% (372)	8.3% (12)	19.8% (14)
Received medical treatment	0.4% (36)	4.0% (6)	5.6% (4)
Current medical treatment	0.1% (9)	0.8% (1)	1.6% (1)
Ever misused	0.1% (7)	0.8% (1)	2.9% (2)
Narcolepsy			
Lifetime diagnosis	1.0% (100)	4.0% (6)	5.2% (4)
Received medical treatment	0.3% (34)	1.9% (3)	5.2% (4)
Current medical treatment	0.1% (10)	0.6% (1)	2.0% (1)
Ever misused	0.03% (3)	0.7% (1)	0

Note. PCE = pharmacological cognitive enhancement. PME = pharmacological mood enhancement; PNE = pharmacological neuroenhancement.

3.5 Discussion

This study aimed to identify the predictors of PCE and PME separately to determine different user groups using two explanation models that focused on self-medication. The first *moderate self-medication* hypothesis stating that frequent and long-term stress predicts PCE and PME was confirmed.

Surprisingly, the second *moderate self-medication* hypothesis, that time pressure and work-related negative stressors would increase the likelihood of PCE, was rejected. In particular, no direct link was found between acute work- or study-related environmental stressors and PCE. These stressors seemed manageable and were not predictors of PCE and

PME, whereas frequent and long-term stress and currently impaired mental health were more likely to predict drug use for PCE and PME. No matter whether PCE is considered as a coping strategy for stress or as part of a certain planning strategy of users, PCE use seems to occur most likely when no other effective alternative is promising for lasting changes of a somehow uncomfortable situation. As intermittent stress is sometimes resolved automatically, it might be less associated with finding new strategies to cope with, such as PCE, or with changing the planning behavior. However, our data rely on self-report and perceived stress can vary strongly between individuals depending on the cognitive appraisal of stress (Lazarus, 1984). Moreover, PCE might be perceived as a short-term solution to reduce long-term stress in people with insufficient personal and social resources required to meet certain demands in the long-term. This is in line with the finding that students who reported having used drugs to improve performance while studying had difficulties to meet the study demands and perceived persistently high performance pressure (Maier et al., 2013; Middendorff et al., 2012). Moreover, pronounced procrastination and high cognitive test anxiety, both characteristics that support chronic stress, increased the willingness to use drugs for PCE among students (Sattler et al., 2014).

Consistent with previous studies, the present findings support the third *moderate self-medication* hypothesis that PCE and PME are associated with illegal drug use (Arria et al., 2008; McCabe et al., 2005). Cannabis users were three times more likely to report PCE and five times more likely to report PME. A recent longitudinal study showed the strong link between cannabis use and mood disorders and suggested that cannabis was used as *self-medication*, similar to the definition of PME in the present study (Feingold et al., 2014). The use of illegal drugs other than cannabis was positively associated with PCE but not with PME. This finding might be explained by the presence of male participants with high levels of sensation seeking in the group (Rabiner et al., 2009a). Additionally, individuals with a history of illegal drug use might be less afraid of the unknown effects and side effects of prescription drugs used for PCE because they are generally used to deal with the uncertainty regarding effects and side effects. However, they might even be more likely to use illegal drugs they usually use recreationally also for cognitive or mood enhancement. This would then question the inclusion of past-year illegal substance use as predictor variable in our model. Nevertheless, when considering the low number of illegal drug users reported having ever used the illegal drug for direct cognitive or mood enhancement (Table 6 in Maier et al., in press), the inclusion is supposed to be accurate. Importantly, alcohol and cannabis use to relax after stress at work or in education was far more prevalent (Maier et al., in press). This is

consistent with the finding of Middendorff and colleagues (2012) whose study revealed that one quarter of PNE users used cannabis to cope with the study demands. However, cannabis users in the present study had most likely not thought about cannabis as a drug used for PNE.

The present findings supported the most specific *moderate self-medication* hypothesis that low self-efficacy would predict PME. Being female and having low self-efficacy were predictors of PME.

Furthermore, the *serious self-medication hypothesis* was confirmed in the analysis, and current medical treatment for a mental disorder, particularly depression and/or an anxiety disorder, was the strongest predictor of both PCE and PME. However, misuse of the treatment medication among patients was rare, and they used illicit substances for PCE or PME in addition to the existing medications to cope with stress and other psychological consequences of their disorders. Medical treatment might be perceived as helpful and effective for coping with the symptoms of the underlying disorder. Hence, the patients might have learned that drugs influence their health outcomes in a positive way, consequently engaging in *serious self-medication* to enhance their performance at work or while studying.

The present findings are in line with Lazarus' (1989) stress theory; PCE and PME are suggested to be stress management strategies for coping with high levels of stress. Consistent with previous research, insufficient coping is assumed to be associated with mental health problems despite or as a consequence of *moderate self-medication* in healthy individuals (Mohr et al., 2014). Moreover, the fact that PCE and PME were frequently used as *serious self-medication* in addition to current medical treatment provides a new perspective on the biomedical ethics debate about PNE. If the target group are not solely healthy people aiming to enhance their performance at work or while studying but also people with mental deficits aiming to perform normal, the impact of PNE on inequalities might differ. In particular, inequality concerns and questions about the possible exacerbation of existing socio-economic inequalities have been raised (Maslen et al., 2014). However, what if people with a mental disorder engage in PNE to reduce the stress and symptoms associated with their disorder and thus enable themselves to perform at a level equal to that of their healthy counterparts? Given that no safe, effective, and highly priced drug for PNE enters the market, the drugs currently discussed as neuroenhancers are available relatively equally to all socio-economic groups. Earp and colleagues (2014) argued that diminishment can be seen as a form of enhancement. Therefore, drug use to diminish certain higher-order capacities that cause the symptoms of a mental disorder can be classified as PNE and is a *serious self-medication* unless it is recommended by a physician. Inevitably, normative questions would need to be used to define

a cut-off point on the continuum between health and disease. However, such a cut-off point does not exist and would not be able to sufficiently take into consideration cultural differences in the concept of health and illness across and even within countries (Laungani, 2007). The absence of this clear cut-off point (Maslen et al., 2014), the individual differences in responses to drugs used for PNE (de Jongh et al., 2008), and the fact that people might obtain the desired prescription or illegal drug from physicians, friends, or via the Internet makes it difficult to legally regulate drug use for enhancement purposes. Maslen and colleagues (2014) suggest that no unambiguous differentiation between treatment and enhancement exists in the vast majority of cases. Therefore, *self-medication* with PCE and PME is also an unsolved issue that needs further consideration. If the bioethical debate is to be moved forward, a better understanding of the strong link between mental health and the non-competitive interests of PCE and PME users needs to be developed.

The few healthy PCE users who were identified showed self-efficacy scale values that were similar to or even higher than those of non-users. For those users, PCE seems to be a lifestyle choice, as Racine and Forlini suggest (2008). PCE users appear to be conscious of their abilities and, in line with the drug instrumentalization theory (Wolff and Brand, 2013), they use the desirable functionalities of psychoactive substances as an additional resource.

Returning to the hypothesis that was posed at the beginning of the study, the findings revealed that both PCE and PME were associated with stress. An unanticipated finding was that time pressure and negative work aspects were not predictors of PCE and PME in the overall model. Only long-term stress and frequent stress predicted PCE and PME. Furthermore, the high prevalence of past-year cannabis use in the PCE and PME users demonstrated that such drug use is likely to be their stress management strategy and a form of *moderate self-medication*.

First, this study is one of the largest studies of pharmacological neuroenhancement, and the weighting procedures used ensured that the results were representative of the Swiss population. Second, participants with a current or past diagnosis of a mental disorder were included in the study, whereas many previous studies only focused on healthy individuals (Barrett et al., 2008). The important mechanism of s*elf-medication* in both healthy and PCE and PME users with mental disorders was unique and progressive. Given that the healthy PCE users in most previous studies were almost all students, the present investigation was the first to consider deficits in PME users in the general population.

The main limitation of the current study is its cross-sectional design, which did not allow the causal associations between the predictors to be conclusively examined. However, the

self-medication hypothesis was supported, which allowed the interpretation of the findings. A further limitation is that the PCE users and the participants who reported both PCE and PME were modeled within one single group to increase the statistical power and strengthen the prediction models. However, the PCE group is the most commonly studied group (Maier and Schaub, 2015; Maslen et al., 2014); therefore, this grouping seems acceptable. Furthermore, regular PCE users show a very specific personality profile (Maier et al., 2015), hence it makes sense to compare this group with nonusers and PME users only. The present study assessed stress at work and in education as possible predictors of PNE. Because of the length of the questionnaire, only single items (no validated scales) were used to assess stress to prevent participant dropouts. Retrospectively, the inclusion of at least one validated stress scale may have increased the predictive power of the overall model.

The understanding of PCE and PME as s*elf-medication* and as functional means of achieving certain ends related to performance or health, as Wolff et al. (2014) suggest, has important implications for further research and policy. The findings of the present study indicate a large gap between healthy, self-confident PNE users experiencing temporary stress and unconfident PNE users with persistently low self-efficacy and high stress or even pathological symptoms. Consistent with previous Swiss studies of PNE, only a small number of healthy people who reported PNE and recreational drug use as a lifestyle choice were found (Maier et al., 2013). Thus, future research should focus on complex problems in disadvantaged individuals (e.g., those with low self-efficacy, insufficient coping strategies, or mental disorders) who self-medicate without or beyond an indicated prescription. A careful diagnosis of mental health disorders, dialogue about treatment options, and investigation of social pressure to perform (e.g., in accordance with the perceived averages of healthy colleagues) might prevent PCE and PME among patients. The communication of risks and medication interactions is strongly recommended to achieve beneficial treatment outcomes regarding the absence of additional *serious self-medication*.

3.6 Conclusions

Various predictor variables for PCE and PME were identified in this study. Consideration of these variables may help identifying potential PCE and PME users for whom measures to prevent drug abuse and manage stress are most appropriate. Furthermore, causal theories concerning engagement in PCE and PME might be examined in longitudinal studies taking into account the identified predictors. Especially *serious self-medication* but also moderate

self-medication seem to be suitable candidates for disentangling causal explanations for engagement in PCE and PME and thus advancing the neuroenhancement debate.

4 Pharmacological Cognitive Enhancement: A Compensation for Cognitive Deficits or a Question of Personality?

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Author contributions

BBQ and MPS conceived the initial idea for this study and all authors contributed to its planning, including defining the aims, variables of interest, in- and exclusion criteria, and analysis strategy. BBQ and MW were responsible for the neuropsychological assessment of the study participants. Qualitative urine and hair testing was performed by ATR and MRB. Statistical analyses were conducted by MW and LJM under the supervision of BBQ and MV, but all authors had access to the data and the statistical outputs. LJM and BBQ have drafted the article and all authors contributed to revisions and approved the final manuscript.

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4.1 Abstract

The ongoing bioethical debate on pharmacological cognitive enhancement (PCE) in healthy individuals is often legitimated by the assumption that PCE will widely spread and become desirable for the general public in the near future. This assumption was questioned as PCE is not equally save and effective in everyone. Additionally, it was supposed that the willingness to use PCE is strongly personality-dependent likely preventing a broad PCE epidemic. Thus, we investigated whether the cognitive performance and personality of healthy individuals with regular nonmedical methylphenidate (MPH) use for PCE differ from stimulant-naïve controls. Twenty-five healthy individuals using MPH for PCE were compared with 39 age-, sex-, and education-matched healthy controls regarding cognitive performance and personality assessed by a comprehensive neuropsychological test battery including social cognition, prosocial behavior, decision-making, impulsivity, and personality questionnaires. Substance use was assessed through self-report and quantitative hair and urine analyses. Recently abstinent PCE users showed no cognitive impairment but superior strategic thinking and decision-making. Furthermore, PCE users displayed higher levels of impulsivity, novelty seeking, and Machiavellianism combined with lower levels of social reward dependence and cognitive empathy. Finally, PCE users reported a smaller social network and exhibited less prosocial behavior in social interaction tasks. In conclusion, the assumption that PCE use will soon become epidemic is not supported by the present findings as PCE users showed a highly specific personality profile that shares a number of features with illegal stimulant users. Moreover, regular MPH use for PCE is not necessarily associated with cognitive deficits.

4.2 Introduction

Prescription stimulants such as methylphenidate (MPH) are controversially discussed as potential drugs for pharmacological cognitive enhancement (PCE) in healthy individuals [1–5]. The increase of MPH prescriptions in the past two decades was supposed to coincide with an increased nonmedical use of MPH for PCE and relatively high prevalence rates of PCE among college students seemed to confirm the prediction [6,7]. However, many studies failed to clearly define "nonmedical use" and considered different substances for PCE impeding the interpretation of the results [8]. Nevertheless, PCE is much more prevalent in the United States compared to Europe [8], but in both regions, MPH is the most frequently misused prescription drug for PCE [1,9].

MPH elevates the neurotransmission of dopamine and noradrenalin by reuptake inhibition at the respective monoamine transporters, and was proposed to influence executive functions and working memory in healthy individuals [10,11]. However, potential benefits and risks of PCE are both modulated by individual differences in response to drugs further depending on drug dose and task requirements. Consequently, procognitive effects of MPH are baseline-dependent (e.g., amelioration at low and impairment at high baseline performance) and afflicted with several trade-offs (e.g., improvement in one cognitive domain with the cost of impairments in other cognitive domains) as well as psychiatric side-effects [10–14].

The use of MPH for the treatment of ADHD is well-established and the potential side-effects are justified by the proven effectiveness [15]. However, this does not reclaim the use by healthy individuals without cognitive deficits. So far, it is unclear whether regular MPH use for PCE in healthy individuals is related to negative long-term cognitive, psychopathological, and neurobiological consequences [10,14]. Nonetheless, previous studies found a higher prevalence of PCE among students with lower grades [1,16,17]. In general, the misuse of prescription stimulants might be associated with neuropsychological deficits prior to or as a consequence of PCE. Reske and colleagues found that occasional prescription stimulant users showed enhanced verbal fluency but, at the same time, more deficits in verbal learning, memory, and cognitive flexibility compared to stimulant-naïve controls. Therefore, they suggested that pre-existing cognitive deficits and subtle executive dysfunctions might be predictors for stimulant use [18,19]. On the other hand, PCE itself might cause drug induced cognitive impairments as shown in a recent longitudinal study with recreational cocaine users [20]. Accordingly, the use of MPH might affect neuroplasticity and may, therefore, alter cognitive function, behavior, and personality of users [21].

Like amphetamine, MPH is a phenylethylamine derivate but shares the mechanism of catecholamine reuptake inhibition with cocaine [10]. The Zurich Cocaine Cognition Study (ZuCo2St) revealed that not only dependent but also recreational cocaine users showed significant deficits in the cognitive domains of attention, working and long-term memory, and executive functions [22]. Cocaine users also revealed higher levels of self-reported impulsivity and novelty seeking and more ADHD symptoms compared to stimulant-naïve controls [22,23]. Moreover, cocaine use was associated with reduced neural sensitivity to social reward potentially explaining the users' deficits in social interactions such as less emotional empathy and a smaller social network [24,25]. Studies considering the nonmedical use of MPH in healthy individuals have only addressed acute MPH effects on social cognition and behavior [26,27], while the effects of chronic MPH use on social behavior are unknown so far.

The bioethical debate on neuroenhancement is based on the assumption that the use of putatively neuroenhancing stimulants already appears to be highly popular and that PCE use will further spread in the near future. However, these assumptions have been recently disputed [14,28]. One argument against a future epidemic of PCE is that not everyone is equally interested in cognitive enhancement [29] assuming that personality has an essential impact on the willingness to use PCE [14]. Surprisingly, the influence of personality on the preference of PCE has scarcely been investigated yet, but Quednow proposed that in particular narcissistic and ambitious people might be more interested in PCE [14]. Preliminary data recently suggested that PCE is positively associated with ADHD symptoms, sensation seeking, and impulsivity [17,30]. As the research on the so-called "dark triad" of personality traits revealed that subclinical narcissism is closely related to Machiavellianism and subclinical psychopathy [31], manipulative, opportunistic, and antisocial behaviors might be potential personality features of PCE users as well.

The primary goal of the present study was, therefore, a broad characterization of recently abstinent PCE users regarding their cognitive, behavioral, and personality profile. Based on previous studies showing a higher prevalence of PCE in students with lower grades [1,16,17] and demonstrating cognitive impairment in cocaine and other stimulant drug users [18–20,22], we hypothesized that MPH misuse for PCE is associated with lower cognitive performance. Moreover, in PCE users we expected an increase in psychopathological loads and a specific personality structure similar to recreational stimulant users [23,25,32]. Specifically, we expected that PCE users show more pronounced narcissistic, opportunistic, Machiavellian, and impulsive facets, and less prominent sociable and prosocial behaviors.

4.3 Methods

4.3.1 Participants

Participants were recruited through flyer advertisements at the University of Zurich and the Swiss Federal Institute of Technology in Zurich, internet advertisement, and via e-mail as study participants from an earlier study on PCE had consented to be contacted again [9]. All participants had to pass an initial telephone screening to assess basic eligibility before they were invited for the assessment at the Psychiatric Hospital of the University of Zurich. Recently abstinent PCE users had to meet the following inclusion criteria: regular MPH use explicitly for PCE during the past 6 months and lifetime use of MPH for PCE on at least 25 occasions. Further inclusion criteria for all participants were 20 to 50 years of age and sufficient knowledge of German language. Exclusion criteria for all participants implied the following conditions: 1) severe medical diseases such as cardiovascular diseases, cancer, HIV, hepatitis, and diabetes; 2) present or prior axis-I psychiatric disorder according to DSM-IV; 3) no family history of a severe DSM-IV psychiatric disorder such as schizophrenia, bipolar disorder, or obsessive-compulsive disorder; 4) lifetime history of a neurological disorder such as meningitis, epilepsy, Tourette syndrome, Parkinson's disease, dementia, and head injury including loss of consciousness for more than 30 sec; 5) lifetime history of heroin use; 6) daily use of cannabis; 7) regular use of prescription drugs with effects on the central nervous system; and 8) use of other illegal drugs not mentioned before on more than 50 occasions. Prior to the testing session, participants had to abstain from MPH and illegal drugs for at least 72 hours and from alcohol for 24 hours. Adherence with these instructions was assessed by urine testing as described before [22]. The study was approved by the Cantonal Ethics Committee of Zurich. All study participants provided informed consent after being fully informed about the study details.

4.3.2 Drug use

Current and past use of illegal substances and prescription drugs was assessed by a standardized Interview for Psychotropic Drug Consumption considering the date of last use, average quantity (mg, g, tablets, etc.) used weekly, and total lifetime duration of use [33]. Moreover, urine and hair testing revealed objective quantitative results about recent and past drug use. Urine samples were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) regarding MPH and ritalinic acid (S1 Method) and by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany) for all other drugs [22]. MPH and illegal drug use during the past 6 months was

assessed by 6-cm hair samples analyzed by LC-MS/MS as described in detail in S2 Method [22].

4.3.3 Cognition

For matching reasons, premorbid verbal intelligence was assessed by the Multiple-Choice Vocabulary Test (MWT-B). The following classical neuropsychological tests were used to assess cognition of PCE users and stimulant-naïve controls: four tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB) were used to test sustained attention (Rapid Visual Processing, RVP), visuo-spatial memory (Paired Associates Learning, PAL), Spatial Working Memory (SWM), and Intra-Extra-Dimensional Set-Shifting (IED); the Letter-Number-Sequencing Task (LNST) was used to test verbal working memory; and the Rey Auditory Verbal Learning Test (RAVLT) was applied to test declarative verbal memory functions. Similar to our previous studies with cocaine users, four main z-scored cognitive domains (attention, working memory, declarative memory, executive functions) were defined and equally integrated in a global cognitive index (GCI, for details regarding the construction of the cognitive domains see S3 Method) [20,22]. Furthermore, the Iowa Gambling Task (IGT) was used to measure decision-making. Points gained in the IGT were converted into Swiss Francs and disbursed to the participants.

4.3.4 Social cognition, interaction, and function

Social cognitive functions such as cognitive and emotional empathy as well as theory-of-mind (ToM) were assessed with the Multifaceted Empathy Test (MET) and with the Movie for the Assessment of Social Cognition (MASC), respectively. Moreover, the Distribution Game and the Dictator Game tested social decision-making in an interaction paradigm, while the Social Network Questionnaire (SNQ) provided the number of currently available social contacts. Points gained in both interactive games were converted into Swiss Francs and disbursed to the participants. All tests have been described in detail before [24,25].

4.3.5 Personality and psychiatric symptoms

Psychiatric symptoms and personality disorders were assessed using the ADHD Self-Rating scale (ADHS-SR), the Structured Clinical Interview for DSM-IV Axis I (SCID-I Interview) and Axis II (SCID-II Questionnaire), and the Beck Depression Inventory (BDI). The Barratt Impulsiveness Scale (BIS-11), the Temperament Character Inventory (TCI), and the Machiavellianism questionnaire (MACH-IV) were included to assess personality. Additionally, the Delay Discounting task (DD) was used to assess delay of

gratification/reward impulsivity (references to the neuropsychological tasks and all questionnaires are provided in S3 Table).

4.3.6 Statistical analysis

PCE users were matched with stimulant-naïve controls on the following variables: age, sex, years of education, proportion of students, verbal intelligence, and proportion of smokers. Quantitative data were analyzed by independent t-tests in order to compare PCE users with controls. For qualitative data, Chi^2-tests were applied. Person's product moment correlations were used to evaluate the association between MPH use, cognitive performance, and personality scores and to explore inter-correlations between variables with significant group differences. All statistical analyses were conducted using SPSS Statistics 22 (Dynelytics, Zurich, Switzerland). For group comparisons, $p < 0.050$ was set as the significance level, while for correlation analyses the significance threshold was set at $p < 0.010$ in order to avoid an accumulation of alpha-error.

4.4 Results

Ninety-four PCE users contacted us and showed interest in study participation. After a careful telephone screening, we were able to test 32 regular PCE users but only 25 of them met all inclusion criteria and were included in the final analyses (the trial profile is shown in Fig. 3). PCE users were matched with 39 stimulant-naïve controls that were tested in the same way. As intended by the matching procedure both groups did not differ regarding age, sex, student status, years of education, verbal IQ, and smoking status, but PCE users reported significantly more ADHD symptoms than controls (Table 11). According to the cut-off of the ADHS-SR questionnaire, five PCE users potentially met the DSM-IV criteria for ADHD but have not been diagnosed with this disorder before and were thus included in the study.

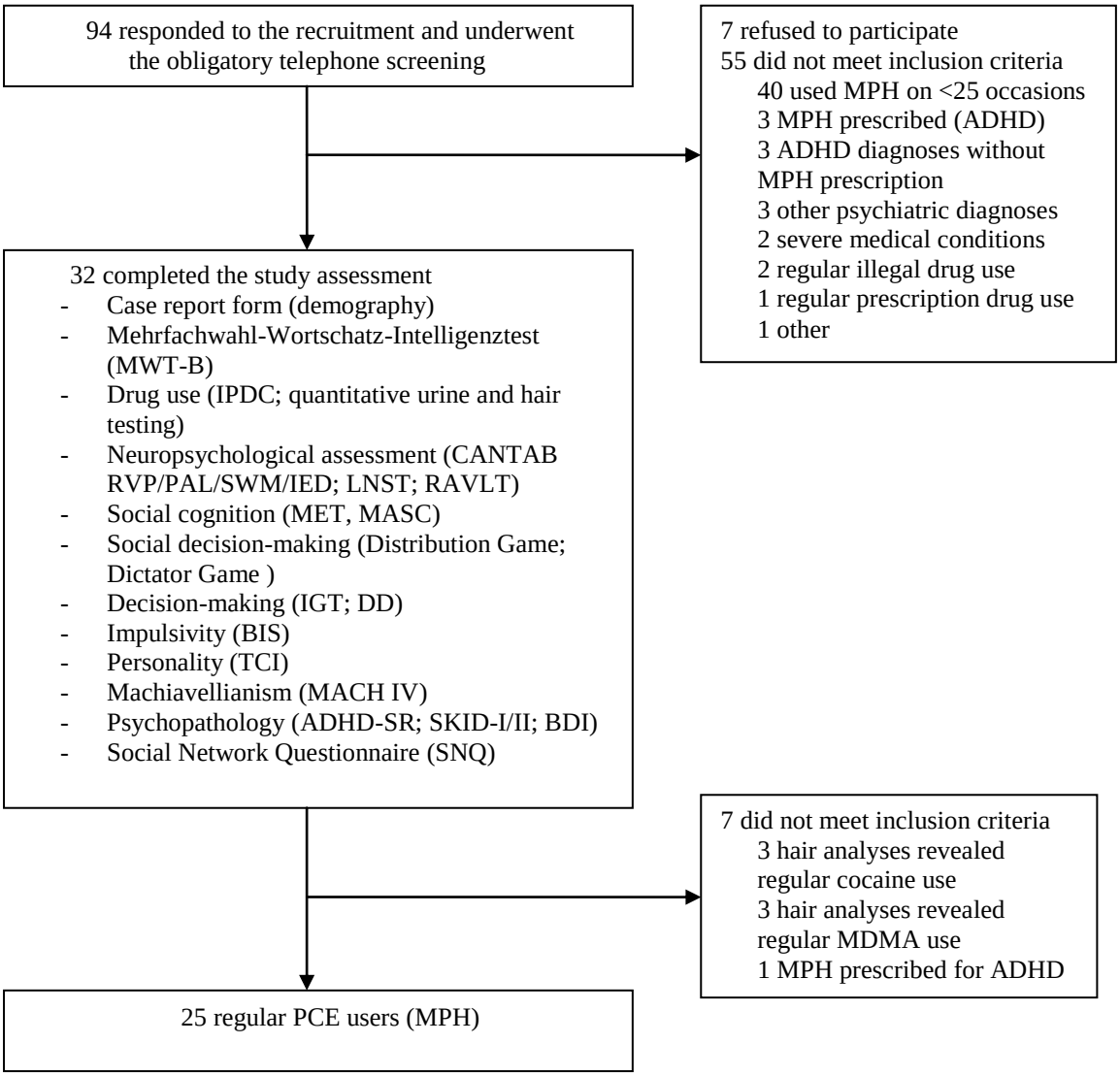

Figure 3. Trial profile.

ADHD: Attention Deficit Hyperactivity Disorder, ADHD-SR: Attention Deficit Hyperactivity Disorder Self-Rating scale, BIS-11: Barratt Impulsiveness Scale-11, CANTAB: Cambridge Neuropsychological Test Automated Battery, DD: Delay Discounting task, IDPC: standardized Interview for Psychotropic Drug Consumption (self-report), IED: Intra-Extra Dimensional Set-Shifting, IGT: Iowa Gambling Task, LNST: Letter Number Sequencing Task, MASC: Movie for the Assessment of Social Cognition, MET: Multifaceted Empathy Test, MDMA: 3,4-Methylendioxy-N-methylamphetamin, MPH: methylphenidate, PAL: Paired Associates Learning, PCE: pharmacological cognitive enhancement, RAVLT: Rey Auditory Verbal Learning Test, RVP: Rapid Visual Information Processing, SCID I/II: Structural Clinical Interview for DSM-IV Axis I/II Disorders, SWM: Spatial Working Memory, TCI: Temperament and Character Inventory.

Table 11. Demographic characteristics and drug use of stimulant-naïve healthy controls and individuals using methylphenidate for the purpose of pharmacological cognitive enhancement (PCE)

	Controls (n=39)	*PCE users (n=25)*	*X^2 / t-test*	*df*	*p value*
Demographics					
Age	26.2 (5.4)	24.0 (3.0)	1.185	62	0.072
Women	18 (46%)	11 (44%)	0.029	1	0.866
Smoking status (yes)	24 (46%)	15 (44%)	0.029	1	0.866
Student status (yes)	26 (67%)	20 (80%)	1.340	1	0.247
Years of education	11.6 (1.5)	12.0 (1.0)	-1.161	62	0.250
Verbal IQ (MWT-B)	106.0 (8.6)	104.8 (10.5)	0.507	62	0.614
ADHD-SR (range 0-54)	7.3 (5.1)	12.9 (8.5)	-3.303	62	**0.002**
BDI sum score	3.5 (4.2)	4.8 (5.2)	-1.029	62	0.308
Drug use					
Methylphenidate					
Tablets per week (10mg)	0	2.5 (3.2)			
Years of use	0	2.8 (1.5)			
Cumulative dose (tablets)	0	485.6 (1044.4)			
Last consumption (days)	NA	40.5 (52.2), *n*=24			
Hair analysis (pq/mg)	0	84.2 (199.1)			
Alcohol					
Grams per week	90.6 (77.0)	92.8 (76.0)	-0.114	62	0.910
Years of use	8.6 (5)	7.2 (3.5)	1.309	62	0.195
Tobacco					
Cigarettes per day	5.6 (8.0)	4.8 (6.4)	0.456	62	0.650
Years of use	5.9 (6.3)	3.7 (3.6)	1.557	62	0.125
Cannabis					
Grams per week	0.2 (0.7)	0.2 (0.4)	0.570	62	0.571
Years of use	3.7 (4.4)	3.3 (3.5)	0.385	62	0.702
Cumulative dose (grams)	965.4 (4423.9)	101.3 (164.0)	0.973	62	0.334
Last consumptions (days)	740.6 (1735.0), *n*=24	23.5 (24.3), *n*=13	1.480	35	0.148
Positive urine testing[a]	4 (10%)	2 (8%) [a]	0.064	1	0.801
Cocaine					
Grams per week	0	0.1 (0.2)	-1.566	62	0.122
Years of use	0 (0)	1.1 (2.8)	-2.499	62	**0.015**
Cumulative dose (grams)	0.2 (0.9)	15.8 (60.4)	-1.620	62	0.110
Last consumptions (days)	1104.8 (947.9), *n*=3	319.2 (326.4), *n*=9	2.290	10	**0.045**
Positive urine testing[a]	0	0			
Positive hair testing[a]	0	1 (4%)	1.585	1	0.280
Amphetamine					
Grams per week	0	0.01 (0.02)	-1.718	62	0.091
Years of use	0 (0)	0.4 (1.3)	-2.064	62	**0.043**
Cumulative dose (grams)	0.003 (0.02)	0.6 (2.4)	-1.441	62	0.155
Last consumptions (days)	547.2 (258.0), *n*=2	346.4 (724.9), *n*=6	0.367	6	0.726
Positive urine testing[a]	0	1 (4%)	1.651	1	0.199
Positive hair testing[a]	0	1 (4%)	1.585	1	0.280
MDMA					
Tablets per week	0	0.04 (0.2)	-1.399	62	0.167
Years of use	0 (0)	0.4 (1.0)	-2.342	62	**0.022**
Cumulative dose (tablets)	0.13 (0.4)	3.4 (9.0)	-2.256	62	**0.028**
Last consumption (days)	3100.8 (1289.8), *n*=2	31.3 (26.0), *n*=3	3.976	6	**0.007**
Positive hair testing[a]	0	2 (8%)	3.221	1	0.073

Data are means and standard deviations, or number and percent. Significant p-values are shown in bold. [a]For cut-offs see S1 and S2 Methods. ADHD-SR: Attention Deficit Hyperactivity Disorder Self-Rating scale, BDI: Beck Depression Inventory, IQ: intelligence quotient, MWT-B: Mehrfachwahl-Wortschatz-Test (vocabulary test), PCE: pharmacological cognitive enhancement.

On average, PCE users reported the intake of MPH for PCE since 2.8 years, used 2.5 tablets with 10mg MPH per week, have taken 486 MPH tablets in their lifetime, and were abstinent from MPH since 41 days (Table 1). Six PCE users featured positive urine testing for ritalinic acid (mean 248ng/ml, range 3-1312 ng/ml), while only one PCE user revealed small traces of MPH (14 ng/ml). Self-reported weekly MPH use was significantly correlated with hair concentrations of MPH over the past 6 months ($r = 0.640$, $p < 0.001$, $n = 25$).

PCE users showed no significant differences in the four cognitive domains and the GCI compared to controls (Fig. 4).

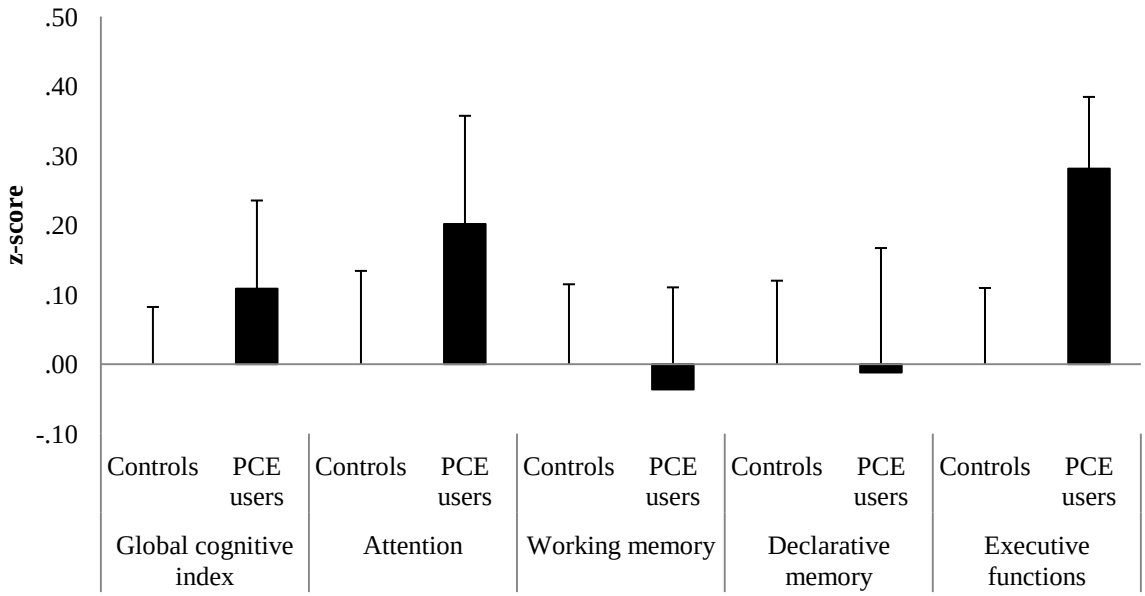

Figure 4. Mean z-scores and standard errors for the global cognitive index (GCI) and four cognitive domains.

However, the executive functions showed a moderate effect size ($d = 0.44$) with regard to a superior performance of the PCE users, which was mainly explained by a significantly better performance in the strategy subscore of the SWM (S4 Table). In the IGT, PCE users gained more points in a shorter time (Fig. 5), showing better performance in the second and in the fourth quartile (Fig. S1).

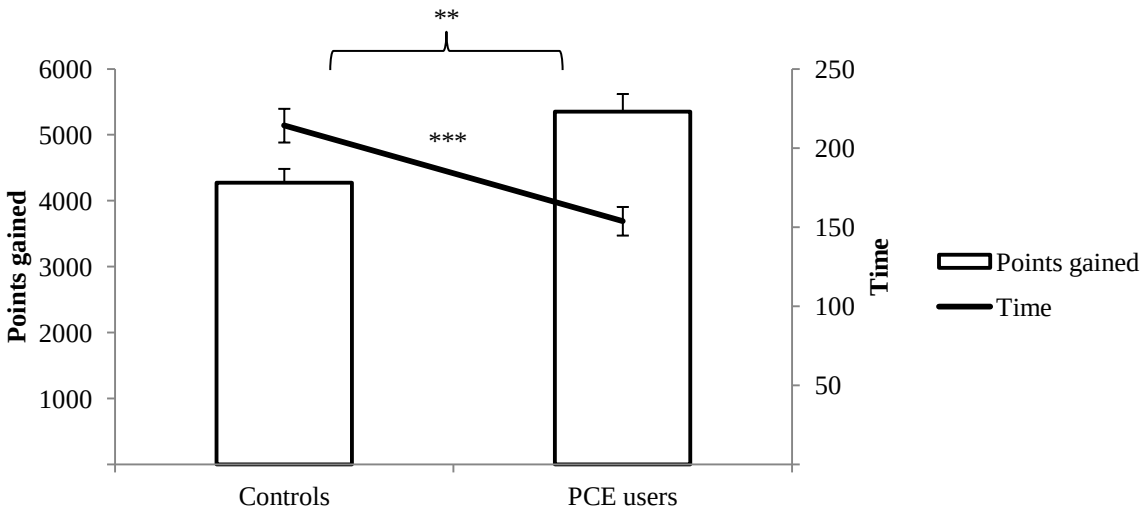

Figure 5. Means and standard errors of points gained and of processing time (sec) in the Iowa Gambling Task (IGT). **p < 0.010, and *** p < 0.001.

PCE users displayed higher levels of novelty seeking (mainly explained by significantly higher disorderliness) and revealed lower scores in social reward dependence (primarily due to significantly lower sentimentality) compared to controls. No group differences were found for delay discounting, but PCE users showed elevated self-reported impulsivity in the BIS-11 (specifically in the attention subscores), higher negativistic and antisocial personality traits in the SCID-II questionnaire, as well as higher Machiavellianism in the MACH-IV (Table 12). Compared to controls, PCE users reported significantly fewer social contacts and their decisions in the social interaction tasks were more self-serving as they preferred higher monetary payoffs for themselves (Table 12). When assessing mental perspective-taking (ToM), PCE users made somewhat fewer errors in the MASC but the difference was not significant. Although PCE users revealed a slightly enhanced mental perspective-taking in the MASC, they showed, however, significantly lower cognitive empathy in the MET, indicating worse emotion recognition from complex picture material (Table 12).

Table 12. Personality traits of stimulant-naïve healthy controls and individuals using methylphenidate for the purpose of pharmacological cognitive enhancement (PCE)

	Controls (n.=.39)	*PCE users (n.=.25)*	*t-test*	*df*	*p value*	*Cohen's d*
Personality						
BIS-11 sum score	61.6 (8.4)	66.8 (11.0)	-2.145	62	**0.036**	0.53
BIS-11 Motor impulsiveness	21.7 (3.1)	23.9 (6.0)	-1.941	62	0.057	0.49
BIS-11 Nonplanning impulsiveness	25.4 (4.2)	26.2 (5.1)	-0.690	62	0.493	0.18
BIS-11 Attentional impulsiveness	14.6 (3.2)	16.8 (4.4)	-2.293	62	**0.025**	0.57
BIS-11 Attention	9.5 (2.3)	11.1 (2.8)	-2.428	62	**0.018**	0.60
BIS-11 Cognitive Inflexibility	5.1 (1.7)	14.2 (3.3)	-1.284	62	0.204	0.33
TCI Novelty Seeking	21.8 (5.2)	24.6 (5.9)	-2.003	62	**0.050**	0.50
TCI Exploratory excitability	7.9 (2.0)	8.3 (2.5)	-0.804	62	0.425	0.21
TCI Impulsiveness	4.3 (2.1)	4.6 (2.2)	-0.563	62	0.576	0.14
TCI Extravagance	5.4 (1.8)	5.9 (1.9)	-0.946	62	0.348	0.24
TCI Disorderliness	4.2 (1.8)	5.8 (1.7)	-3.566	62	**0.001**	0.84
TCI Harm avoidance	14.3 (5.6)	13.2 (6.9)	0.747	62	0.458	0.19
TCI Reward Dependence	16.9 (4.0)	14.6 (4.2)	2.182	62	**0.033**	0.54
TCI Sentimentality	6.5 (1.8)	5.4 (1.8)	2.299	62	**0.025**	0.57
TCI Attachment	6.5 (1.9)	5.5 (2.4)	1.850	62	0.069	0.47
TCI Dependence	4.0 (1.6)	3.7 (1.6)	0.565	62	0.574	0.15
TCI Persistence	4.3 (2.1)	3.4 (2.1)	1.681	62	0.098	0.42
TCI Self-Directedness	33.9 (6.0)	31.2 (6.4)	1.704	62	0.093	0.43
TCI Cooperativeness	33.5 (5.7)	31.5 (5.0)	1.375	62	0.174	0.35
TCI Self-Transcendence	10.2 (5.2)	9.2 (6.6)	0.695	62	0.490	0.18
SCID-II Avoidant	1.2 (1.4)	0.7 (1.1)	1.526	62	0.132	0.39
SCID-II Dependent	1.2 (1.1)	1.2 (1.0)	-0.035	62	0.973	0.01
SCID-II Obsessive-compulsive	3.5 (1.8)	3.6 (1.6)	-0.256	62	0.799	0.07
SCID-II Negativistic	1.2 (1.4)	2.0 (1.4)	-2.486	62	**0.016**	0.61
SCID-II Depressive	1.1 (1.6)	1.4 (1.7)	-0.559	62	0.578	0.14
SCID-II Paranoid	1.6 (1.8)	1.8 (1.9)	-0.359	62	0.721	0.09
SCID-II Schizotypal	1.3 (1.6)	1.1 (1.0)	0.628	62	0.532	0.16
SCID-II Schizoid	0.7 (1.1)	1.2 (1.3)	-1.699	62	0.094	0.43
SCID-II Histrionic	1.9 (1.5)	2.5 (1.9)	-1.343	62	0.184	0.34
SCID-II Narcissistic	2.4 (2.5)	3.2 (2.3)	-1.241	62	0.219	0.32
SCID-II Borderline	2.4 (2.1)	2.3 (2.0)	0.303	62	0.763	0.08
SCID-II Antisocial	1.9 (1.6)	3.0 (2.7)	-2.011	62	**0.049**	0.50
Social cognition and interaction						
MACH-IV sum score	89.7 (12.3)	97.0 (10.5)	-2.561	61	**0.013**	0.64
DD *k* parameter all	0.012 (0.018)	0.022 (0.032)	-1.615	62	0.111	0.41
MET Direct Empathy	5.1 (1.2)	4.7 (1.2)	1.426	62	0.159	0.36
MET Indirect Empathy	4.8 (1.2)	4.6 (1.3)	0.420	62	0.676	0.11
MET Cognitive Empathy	25.4 (3.8)	23.0 (4.9)	2.273	62	**0.026**	0.56
MASC Total ToM errors	10.2 (4.6)	8.2 (3.2)	1.905	62	0.061	0.48
Social network size (SNQ)	21.5 (7.3)	17.8 (5.3)	2.213	62	**0.031**	0.55
Distribution game, payoff player B	19.0 (8.0)	17.0 (9.6)	0.882	62	0.381	0.23
Dictator game, payoff player B	16.6 (12.2)	10.3 (9.4)	2.196	62	**0.032**	0.55

Data are means and standard deviations. Significant p-values are shown in bold. BIS: Barratt Impulsiveness Scale, DD: Delay Discounting task, MACH-IV: Machiavellianism Scale, MASC: Movie for the Assessment of Social Cognition, MET: Multifaceted Empathy Test, PCE: pharmacological cognitive enhancement, SCID-II: Structural Clinical Interview for DSM-IV Axis-II Disorders, SNQ: Social network questionnaire, TCI: Temperament and Character Inventory, ToM: Theory-of-Mind.

Neither cognitive performance nor personality scales were correlated with any MPH consumption parameters, indicating that the shown abnormalities of PCE users are likely not drug-induced. Machiavellianism was positively correlated with the TCI novelty seeking subscore disorderliness and the SCID-II negativistic score but negatively correlated with TCI social reward dependence and its subscore sentimentality. Not surprisingly, the ADHS-SR score was highly correlated with several BIS-11 scores but also with the SCID-II negativistic score. TCI disorderliness and the SCID-II antisocial score were positively correlated as well (S3 Table). These correlations reflect overlapping concepts of impulsivity and sociability as measured by the different questionnaires.

4.5 Discussion

The aim of the study was to investigate whether regular PCE users show impaired cognitive functions and a specific pattern of personality traits. The study revealed two main findings: 1) recently abstinent PCE users and stimulant-naïve controls performed equally in most of the cognitive tasks but PCE users performed better in strategic thinking and decision-making, and 2) PCE users showed higher impulsivity, higher novelty seeking, higher Machiavellianism, and more pronounced antisocial and negativistic personality traits, in combination with lower social reward dependence compared to controls. In line with this personality pattern, they behaved more opportunistically in social interaction tasks, showed less cognitive empathy, and reported having a smaller social network. Importantly, these results cannot be explained by withdrawal effects as the mean abstinence duration from MPH was 41 days and only one subject has shown very small traces of MPH in the urine testing.

The finding that regular PCE users showed elevated attentional impulsivity but no cognitive impairment might indicate their motivation to use MPH for PCE. As it was shown that only individuals with low baseline performance show cognitive improvements using stimulant drugs [34], it is unlikely that MPH actually improved general cognitive functioning of the present PCE users because they already performed very well and sometimes better than controls. However, MPH is effective to treat symptoms of ADHD such as attentional impulsivity [10]. In fact, PCE users in the present study showed more ADHD symptoms and a previous study found procognitive effects of MPH specifically in healthy individuals with high impulsivity [35]. Thus, MPH might improve impulse control of PCE users, helping them to begin and sustain studying, rather than enhancing cognition directly. Consequently, not everyone benefits from MPH use and opposite cognitive effects (improvement and impairment) of the same MPH dose might even occur in the same individual depending on

task requirements [10,13]. As a specific predisposition such as high impulsivity is needed to benefit from MPH use and not everyone is willing to use PCE anyway [29], a forthcoming epidemic of MPH use for PCE is considered unlikely.

Although the groups did not significantly differ on the SCID-II narcissistic scale as initially hypothesized, PCE users showed more negativistic and antisocial personality traits, and higher Machiavellianism compared to controls. Interestingly, the SCID-II narcissistic subscale was significantly correlated with Machiavellianism (r.=.0.38, p.<.0.010) and the SCID-II negativistic subscale (r.=.0.51, p.<.0.001), confirming that narcissism, negativism, and Machiavellianism show a considerable phenomenological overlap. Thus, PCE users showed a specific pattern of personality traits that has been conceptualized as the "dark triad" [31]. Moreover, with their increased novelty seeking, higher impulsivity, and antisocial tendencies, PCE users share a number of personality features with recreational stimulant users [23,36]. Additionally, PCE users behaved less prosocial in a money distribution game similar to recreational and dependent cocaine users as shown recently [25]. As intensity of cocaine use was not correlated with social decision-making, Hulka et al. suggested that the opportunistic behavior of stimulant users might be a stable trait and possibly a predisposition for the initiation of stimulant use [25]. Furthermore, similar to cocaine users, PCE users also displayed a smaller social network than controls [24]. This might be explained by the fact that PCE users are less sociable (as their personality profile suggests) and, thus, less integrated in social networks. Additionally, the smaller social network might mirror an intensified cost-benefit thinking of PCE users, and a more strategic selection of friends as supported by the present findings in IGT decision-making and strategic thinking.

Our findings are subject to some limitations. First, the number of PCE users was relatively small. This is obviously a threat to the statistical power of the reported analysis but, at the same time, a further implicit result of the study. In fact, it was hard to find individuals with regular MPH use for PCE who reported no concurrent regular use of other illegal drugs and no ADHD diagnosis. Second, the fact that the data were restricted to PCE users, who used MPH without regular co-use of illegal drugs of abuse, is a further limitation as it was shown previously that PCE users show a higher prevalence of illegal drug use compared to non-users [9,17]. Therefore, the question arises, whether we tested only a very unique group within the already very specific group of PCE users. Nevertheless, the exclusion of PCE users with regular illegal drug use was inevitable in order to explain differences between PCE users and controls exclusively by the MPH use. Moreover, previous research revealed that PCE occurs most likely during short periods of exam preparation and daily or high dose use of PCE is rare

[9]. Thus, through our inclusion criteria, we likely skimmed only the most intense PCE users. Third, we used a cross-sectional design but a longitudinal design would have been most appropriate to investigate cause-effect relationships between PCE drug use and changes in cognition and personality.

4.6 Conclusions

This is the first study that broadly characterized individuals regularly using MPH for PCE by applying a comprehensive neuropsychological test battery in combination with a thorough personality assessment and urine and hair testing. Our findings indicate that the regular nonmedical MPH use for PCE over more than two years was not associated with cognitive deficits. PCE users performed equally to controls, or even better in tasks requiring strategic thinking, which disproves the assumption that PCE is a compensation for cognitive deficits [1,16,17]. As the personality profile of PCE users shared some features with recreational illegal stimulant users, such as higher novelty seeking and impulsivity, we propose instead that PCE users may aim to improve their impulse control in order to optimize their own learning compliance. PCE users were also found to be less prosocial, less emphatic, and more Machiavellianism, which is in line with their enhanced strategic thinking and planning behavior. Thus, PCE users may instrumentalize MPH as little helper [37] in order to maximize their own benefits. Finally, the overall personality profile of PCE users is highly specific disproving the often made assumption that PCE will widely spread in society.

Acknowledgments

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4.7 Supplementary material

S1 Method urine testing. Concentration of methylphenidate for the calibration ranged from 2 ng/mL to 1000 ng/mL and concentrations were equally distributed over the concentration range in four calibration solutions. Authentic urine samples were analyzed after protein precipitation (PP). Briefly, 300 µL of urine was mixed with 30 µL of the internal standard mixture containing methylphenidate d9 at 100 ng/mL and 30 µL of the calibration

solution. Afterwards it was shaken for 5 min at 1400 rpm. Then, 900 µL of ice cold acetonitrile was added, and the mixture was shaken for 10 minutes at 1400 rpm and centrifuged for 10 min at 12000 rpm. An aliquot of 600 µL was transferred and evaporated to dryness under a gentle stream of nitrogen at 40°C. The residue was dissolved in 50 µL of a mixture of eluent A (25 mM NH4+ acetate + 0.1% acetic acid in H2O) and eluent B (0.1% acetic acid in acetonitrile). Aliquots of 10 µL of this solution were analysed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The acquisition method was Sequential Window Acquisition of all Theoretical Ion Spectra (SWATH). Quantification of ritalinic acid was done using methylphenidate calibration. For the detection of illegal drug use, the following cut-offs (Administration Substance Abuse and Mental Health Services, 2008) have been applied: Cannabis, 50 ng/ml; cocaine, 150 ng/mg; and amphetamines, 500 ng/ml. Opioids, benzodiazepines, and barbiturates were not detected in our urine samples.

S2 Method hair testing. To characterize drug use over the last six months objectively, hair samples were collected and analyzed with LC-MS/MS. If participants' hair was long enough, one sample of six cm hair (from the scalp) was taken and subsequently divided into two subsamples of three cm length. The following compounds were assessed: cocaine, benzoylecgonine, ethylcocaine, norcocaine, amphetamine, methamphetamine, MDMA, MDEA, MDA, morphine, codeine, methadone EDDP (primary methadone metabolite), tramadol, and methylphenidate. For our routine protocol for drugs of abuse analysis a three step washing procedure with water (2 minutes shaking, 15ml), acetone (2min., 10ml) and finally hexane (2min., 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL hydrochloric acid 33 % (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5. MDEA-d6, MDA-d5, methadone-d9, EDDPd3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland). The LC-MS/MS

apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was 3 performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1 mM formic acid (eluent B). The Analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively. According to the Society of Hair Testing, the following cut-offs ("Recommendations for hair testing in forensic cases.," 2004) have been applied: cocaine, 500 pg/mg; amphetamine, 200 pg/mg; and MDMA, 200 pg/mg. Opioids and other illegal drugs tested above were not detected in our hair samples.

S3 Method construction of the four cognitive domain scores.

Attention To assess attention, we primarily focused on sustained attention by including the two RVP parameters discrimination performance A' and total of hits (Jones, Sahakian, Levy, Warburton, & Gray, 1992). In order to diversify this domain, we further added the RAVLT parameter trial 1, a supraspan measure with a strong attentional component (Lezak, Howieson, Loring, Hannay, & Fischer, 2004).

Working memory The SWM parameter total errors tested the capability to retain spatial information and to manipulate remembered items in the working memory (R. G. Morris et al., 1988). The LNST score measured verbal working memory by summing up the number of correct responses (Crowe, 2000). The PAL first trial memory score measured visual working memory by counting the number of correctly located patterns after the first presentation (Sahakian et al., 1988).

Declarative memory Three RAVLT parameters were included to assess the verbal declarative memory performance: ∑trials 1-5, delayed recall trial 7, and adjusted recognition performance p(A). Furthermore, the two PAL parameters (adjusted total of errors and adjusted total of trials) were used to capture visual declarative memory (Sahakian et al., 1988).

Executive functions First, the SWM strategy score assessed the applied heuristic strategies, (R. G. Morris et al., 1988) a typical feature of the executive functions. Second, the RAVLT recall consistency score is a parameter typically impaired in patients with prefrontal lesions (Benedict et al., 2005; Jokeit et al., 1997), and related with measures of executive functions.(Beebe, Ris, & Dietrich, 2000) Third, the IED was used to assess visual discrimination, attentional set formation, maintenance, shifting, and flexibility (Downes et al., 1989). The considered test parameters were the total of errors and trials adjusted to the amount of completed stages.

Table S3. References to neuropsychological tasks, interviews, and questionnaires used

Test abbreviation	Test name	Reference
Drug use		
IPDC	Interview for Psychotropic Drug Consumption	Quednow et al. (2004)
Cognition		
MWT-B	Mehrfach-Wortwahl-Intelligenztest	Lehrl (1989)
CANTAB	Cambridge Neuropsychological Test Automated Battery	Strauss, Sherman, & Spreen (2006)
RVP	Rapid Visual Processing	Jones et al. (1992)
PAL	Paired Associates Learning	Sahakian et al. (1988)
SWM	Spatial Working Memory	Morris et al. (1988)
IED	Intra-Extra-Dimensional Set Shifting	Downes et al. (1989)
LNST	Letter Number Sequencing Task	Wechsler (1997)
RAVLT	Rey Auditory Verbal Learning Test	Rey (1964); Helmstaedter, Lendt, & Lux (2001)
IGT	Iowa Gambling Task	Bechara, Dolan, & Hindes (2002)
Social cognition, interaction, and function		
MET	Multifaceted Empathy Test	Dziobek et al. (2008)
MASC	Movie for the Assessment of Social Cognition	Dziobek et al. (2006)
SNQ	Social Network Questionnaire	Linden, Lischka, Popien, & Golombek (2007)
Distribution Game	Distribution Game	Engelmann & Strobel (2004)
Dictator Game	Dictator Game	Charness & Rabin (2002)
Personality and psychiatric symptoms		
ADHS-SR	ADHD Self-Rating scale	Rösler et al. (2004)
SCID-I	Structured Clinical Interview for DSM-IV Axis I	Wittchen, Wunderlich, Gruschwitz, & Zaudig (1997a)
SCID-II	Structured Clinical Interview for DSM-IV Axis II	Wittchen, Wunderlich, Gruschwitz, & Zaudig (1997b)
BDI	Beck Depression Inventory	Beck, Steer, & Carbin (1988)
BIS-11	Barratt Impulsiveness Scale	Patton, Stanford, & Barratt (1995)
TCI	Temperament Character Inventory	Cloninger, Przybeck, Svrakic, & Wetzel (1994) Berth, Cloninger, Przybeck, Svrakic, & Wetzel (2001)
MACH-IV	Machiavellianism Test	Christie & Geis (1970)
DD	Delay Discounting Task	Kirby & Petry (2004)

Table S4. Global cognitive index (GCI), the four cognitive domain *z*-scores, and neuropsychological test scores of stimulant-naïve healthy controls and individuals using methylphenidate for the purpose of pharmacological cognitive enhancement (PCE)

	Controls (n.= 39)	*PCE users (n.=25)*	*t-test*	*df*	*p-value*	*Cohen's d*
Global Cognitive Index (GCI)	0 (0.5)	0.1 (0.6)	0.564	62	0.456	0.19
Neurocognitive domain scores						
Attention	0 (0.8)	0.2 (0.8)	0.931	62	0.338	0.25
Working memory	0 (0.7)	-0.04 (0.7)	0.039	62	0.844	0.05
Declarative memory	0 (0.8)	-0.01 (0.9)	0.004	62	0.953	0.02
Executive functions	0 (0.7)	0.3 (0.5)	3.090	62	0.084	0.44
Neuropsychological test scores						
Attention						
RVP Discrimination performance A'	0.9 (0.04)	0.9 (0.04)	-0.484	62	0.630	0.12
RVP Total hits	19.2 (4.5)	19.7 (3.9)	-0.469	62	0.641	0.12
RAVLT Supraspan trial 1	9.9 (2.1)	10.7 (2.5)	-1.347	62	0.183	0.34
Working memory						
LNST Score	16.9 (2.7)	16.4(3.1)	0.631	62	0.530	0.16
SWM Total errors	18.0 (16.6)	12.4 (13.1)	1.402	62	0.166	0.36
PAL First trial memory score	16.7 (3.4)	15.8 (3.7)	1.017	62	0.313	0.26
Declarative memory						
RAVLT Learning performance (∑ trials 1-5)	65.2 (5.1)	65.8 (7.1)	-0.371	62	0.712	0.10
RAVLT Adj. recognition performance p(A)	0.9 (0.1)	0.9 (0.1)	0.499	62	0.619	0.13
RAVLT Delayed recall trial 7	13.8 (1.6)	14.0 (1.4)	-0.704	62	0.484	0.18
PAL Total errors adjusted	7.8 (9.6)	9.3 (9.2)	-0.641	62	0.524	0.16
PAL Total trials adjusted	7.9 (2.7)	8.0 (2.7)	-0.187	62	0.852	0.05
Executive functions						
IED Total errors adjusted	30.0 (38.4)	19.4 (17.9)	1.278	62	0.206	0.33
IED Total trials adjusted	104.0 (68.7)	86.4 (32.1)	1.196	62	0.236	0.31
SWM Strategy score	31.5 (5.9)	28.1 (5.2)	2.363	62	**0.021**	0.58
RAVLT Recall consistency in %	94.3 (5.0)	94.4 (5.6)	-0.068	62	0.946	0.02

Data are means and standard deviations. Significant p-values are shown in bold. IED: Intra-Extra Dimensional Set-Shifting, LNST: Letter Number Sequencing Task, PAL: Paired Associates Learning, PCE: pharmacological cognitive enhancement, RAVLT: Rey Auditory Verbal Learning Test, RVP: Rapid Visual Information Processing, SWM: Spatial Working Memory.

Table S5. Pearson's product-moment correlations between test outcomes and clinical measures of social functioning with significant group differences between stimulant-naïve healthy controls (n = 39) and pharmacological cognitive enhancement users (n = 25)

	SWM strategy score, high performance = low score	Iowa Gambling Task sum score	Iowa Gambling Task time	Machiavellianism	TCI novelty seeking (NS) sum score	TCI NS4 Disorderliness	TCI reward dependence (RD) sum score	TCI RD1 sentimentality	SCID II negativistic	SCID II antisocial	ADHD-SR sum score	BIS-11 sum score	BIS-11 attentional impulsiveness	BIS-11 attention	Dictator game, payoff B	MET cognitive empathy, correct answers	SNQ contacts
SWM strategy score, high performance = low score								0.33**									
Iowa Gambling Task sum score								-0.34**									
Iowa Gambling Task time				-0.49***		-0.41***			-0.33**			-0.39***	-0.32**				
Machiavellianism						0.39**	-0.43***	-0.39**	0.46***								
TCI novelty seeking (NS) sum score						0.73***						0.62***					
TCI NS4 Disorderliness										0.46***		0.52***					
TCI reward dependence (RD) sum score								0.70***	-0.34**								
TCI RD1 sentimentality																	
SCID II negativistic												0.40***	0.38**				
SCID II antisocial																	
ADHD-SR sum score									0.39***			0.56***	0.73***	0.63***			
BIS-11 sum score													0.65***	0.64***			
BIS-11 attentional impulsiveness														0.90***			
BIS-11 attention																	
Dictator game, payoff B																	

Significant partial correlations with a p-level below 1% are shown and marked as: **$p < 0.010$, ***$p < 0.001$. ADHD-SR: ADHD Self-Rating Scale, BIS: Barratt Impulsiveness Scale, MET: Multifaceted Empathy Test, NS: Novelty Seeking, PCE: pharmacological cognitive enhancement, RD: Reward Dependence, SCID I/II: Structural Clinical Interview for DSM-IV Axis I/II Disorders, SNQ: Social Network Questionnaire, SWM: Spatial Working Memory, TCI: Temperament and Character Inventory.

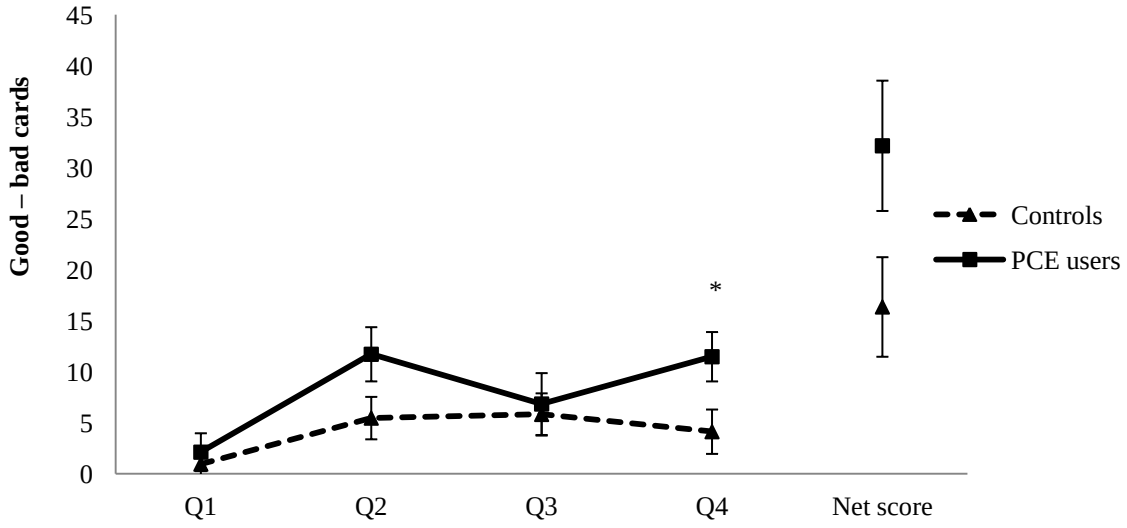

Figure S1. Means and standard errors for quartiles (Q1-Q4) and the net score (good minus bad cards) in the Iowa Gambling Task (IGT); *$p < 0.050$.

5 General Discussion

5.1 Overview of the general discussion

The aim of the present thesis was to determine the prevalence of pharmacological neuroenhancement in Switzerland, considering different motives for use, and to identify predictors and correlates of pharmacological neuroenhancement. The nonmedical use of prescription drugs and the use of alcohol and illegal drugs for the purpose of cognitive and mood enhancement to perform better at work and in education are associated with several risks for physical and mental health. Therefore, this thesis aimed to address various ethical, social, and legal questions related to pharmacological neuroenhancement to make a noteworthy contribution to the current neuroenhancement debate. Additionally, the cognitive, social, and personality characteristics of individuals with regular methylphenidate use for cognitive enhancement were compared to stimulant-naïve controls. Accordingly, directions of further development of pharmacological neuroenhancement in Switzerland were investigated. This final chapter aims to summarize the main findings, strengths, and limitations of the three studies conducted in the present thesis. Because of the findings' relevance for public health issues, important implications for policy, prevention and future research will be discussed.

5.2 Prevalence of and motives for pharmacological neuroenhancement

By using the largest Swiss Internet panel and weighting procedures, the lifetime prevalence of pharmacological neuroenhancement among Swiss employees and students could be determined to be 4.0%, and the 12-month prevalence was found to be 2.1%. Pharmacological mood enhancement was more prevalent than cognitive enhancement or both. Having been diagnosed with a mental disorder, perceived poor health, stress, and illegal drug use were the strongest predictors of pharmacological neuroenhancement. The nonmedical use of tranquilizers and antidepressants to improve mood and relaxation in order to cope with stress at work or in education was more prevalent than the nonmedical use of ADHD medications or other prescription drugs for direct cognitive enhancement. Most individuals using tranquilizers and antidepressants were satisfied with the drug's effect while only a small minority of stimulant users reported that their expectations had been fulfilled. However, the majority of respondents considered the use of prescription drugs and illegal drugs for neuroenhancement as not justifiable, risky, and potentially harmful. Only a small number of the respondents would be willing to use available hypothetically effective neuroenhancement drugs, however, students showed a greater interest in testing such drugs. Illegal drugs were rather used for recreational purposes than for cognitive enhancement at work or in education.

Nevertheless, the use of alcohol and cannabis to reduce stress associated with work or education was prevalent. If this stress coping strategy is functional to improve performance at work or while studying the next day, this use might be classified as neuroenhancement (Maier & Schaub, 2015; Wolff et al., 2014).

In our previous study on pharmacological neuroenhancement among Swiss students, we found that every seventh student had already used prescription drugs, illegal drugs, or alcohol at least once explicitly to enhance cognitive performance while studying (Maier et al., 2013). Consistent with studies among U.S. and European college students, methylphenidate was the prescription drug most frequently misused for pharmacological cognitive enhancement. Nevertheless, alcohol was the substance most often used for enhanced studying performance among Swiss students. For many, it may seem implausible that alcohol, a substance with sedating effects, is used to improve cognitive function as a study aid. However, while alcohol in large doses is rather known to impair memory and cognitive function, low doses have been found to reduce stress-induced impairment of spatial working memory (Gomez, Lewis, & Luine, 2012) and might, therefore, enhance concentration while studying. Moreover, alcohol might be used as a motivational aid to overcome procrastination and start with adverse perceived tasks.

One might claim that the Bologna reform is the reason for the high pressure and large amount of work at universities, and that one cannot cope without using prescription and recreational drugs. Even if the harmonization process of higher educational systems in Europe (Bologna Process; Cumming, 2010) brings new challenges and appears rigorous from the outside, the way to complete a degree has remained similar. What has changed, in particular, is the social expectation in other areas of life. Students do not longer want to spend their whole time in libraries, but they also want to have a satisfied social life (Hildt et al., 2014). In addition, the development of media and the Internet has enabled novel ways of learning and novel options for research. Given the abundance of information and irrelevant distraction, students need to learn to focus on the essential. This uncertainty regarding the required knowledge in combination with high time pressure might create a certain helplessness, which some students might try to counteract by using neuroenhancement. Creating a realistic timetable that considers all examination contents and breaks in between (Dunlosky, Rawson, Marsh, Nathan, & Willingham, 2013), would probably be more effective than using pharmacological neuroenhancement during exam preparation.

Consistent with previous studies, a positive relationship between recreational drug use and the misuse of prescription drugs or illegal drugs for the purpose of neuroenhancement was

found (McCabe et al., 2005; Weyandt et al., 2009). Individuals who used psychoactive substances to achieve better cognitive performance reported more experience with illegal drug use than non-users. This finding was also strengthened by the third study of the present thesis which found that individuals with regular methylphenidate use for cognitive enhancement were likely to be also occasional recreational drug users. To date, there is a lack of studies regarding the direction of the relationship between neuroenhancement and the use of illegal drugs of abuse for recreational purposes. Recreational drug users may be more likely to misuse prescription drugs because they are less afraid of potential side effects of neuroenhancement, since they have experience with side effects of recreational drugs. This hypothesis might be tested in further prospective studies together with a detailed assessment of recurring periods of use and duration of specific substances used for both pharmacological neuroenhancement and recreational use. Since pharmacological neuroenhancement was found to be most prevalent among students, it is of great interest whether the duration of use is limited to student life or whether a transition to working life is likely.

5.3 Predictors of pharmacological neuroenhancement

The second study tested two explanatory models of pharmacological neuroenhancement and found that the serious self-medication model explained far more variance than the moderate self-medication model including stress and self-efficacy. The current medical treatment for a mental disorder was the best predictor of pharmacological neuroenhancement and it was assumed that patients self-medicate beyond their actual prescription in order to perform better at work or while studying. The additional use of prescription and illegal drugs to enhance cognitive performance or mood might aim to increase the effect of prescribed medication, to treat additional symptoms of mental disorders, or to reduce the side effects of indicated medication (Kasten, 1999). When stress and self-efficacy were added to the serious self-medication model, only a little more variance was explained in the overall model. This finding shows the close relationship between stress, self-efficacy, and mental disorders, indicating that most of the stress, which has potentially led to the decision to use pharmacological neuroenhancement, might be explained by the current mental disorder and associated symptoms. The majority of past-year pharmacological mood enhancement users reported having a depression and half of them used prescription drugs to reduce depressive symptoms. Drugs indicated to treat mental disorders were rarely misused. However, other illicit substance use was common, especially among pharmacological cognitive enhancement users. In contrast to former studies that named mostly stress as the result of high workloads

and overwhelming demands as cause for neuroenhancement (Wolff & Brand, 2013), we examined further predictors. Hence we could show that more complex systems underlie pharmacological neuroenhancement and that the prediction of neuroenhancement was best modeled when using a model of serious self-medication.

5.4 Pharmacological cognitive enhancement is a question of personality

In the third study, we found recently abstinent pharmacological cognitive enhancement users and stimulant-naïve controls to perform equally well in most of the cognitive tasks. In addition, cognitive enhancement users performed better in strategic thinking and decision-making. This finding was in contrast to previous research findings which suggested that pharmacological cognitive enhancement aims to compensate deficits such as low grade point average (Franke, Bonertz, et al., 2011; McCabe et al., 2005; Rabiner et al., 2009a). We also found a very specific personality profile of individuals with regular methylphenidate use for cognitive enhancement. Previous research has suggested that healthy cognitive enhancement users might be more ambitious and narcissistic than non-users (Quednow, 2010). Cognitive enhancement users were found to show the dark triad of personality traits (Rauthmann & Kolar, 2012). They exhibit more antisocial and negativistic personality traits, more Machiavellianism and an overlap with narcissism although no significant group differences for narcissism could be found. However, these traits have all beneficial and detrimental trajectories (Rauthmann & Kolar, 2012). Strategic planning and self-serving and less prosocial behavior might be beneficial and sometimes required to succeed in academia. Thus, cognitive enhancement might be perceived as a functional means to achieve good grades or good positions for healthy individuals (Wolff et al., 2014). Despite recent concerns about individualization and a rather narcissistic development in the Western society, no evidence for changes in narcissism and self-enhancement were found when comparing students between 1980 to 2007 (Trzesniewski, Donnellan, & Robins, 2008). This relatively stable proportion of narcissism among students over the years would further dispute the assumption that neuroenhancement will spread in the near future.

5.5 Strengths

The three studies presented in this thesis were unique in their composition and have several strengths worth mentioning. Generally, the studies and their findings would not have achieved the same quality without the continuous review of the rapidly growing literature on

pharmacological neuroenhancement during the time of the thesis. Therefore, the literature body and the careful reflection of its contents is an important strength of this thesis.

The two initial original research articles of this thesis are based on data from one of the largest studies of pharmacological neuroenhancement, and applied weighting procedures used ensured that the results were representative of the Swiss population. No other study in Europe included a representative sample of the general population in their survey to create a national-level estimate of the prevalence of pharmacological neuroenhancement. Instead, previous studies focused on specific groups, such as college students, therefore reporting high prevalence rates of stimulant use for cognitive enhancement based on non-representative survey data. A further strength of the study is that participants with current and past diagnosis of a mental disorder were included in the study, whereas many previous studies only focused on healthy individuals (Barrett et al., 2008).

Addressing the important mechanism of s*elf-medication* in both healthy and disadvantaged neuroenhancement users in the second study was unique and progressive. Every substance use following a certain intention to improve a desirable mental or physical state, without being advised by a doctor, is considered self-medication. Pharmacological neuroenhancement, as self-medication, is a functional means to change a current state which is perceived as unpleasant or insufficient (Wolff et al., 2014). Another important strength of the second study was the discussion of the national data with regard to the non-existent cut-off point on the continuum between health and disease (Laungani, 2007). Specifically designed legal provisions to treat pharmacological neuroenhancement are unreasonable given the absence of this clear cut-off point. Prevention of pharmacological neuroenhancement has to start with the question "why" (Wolff et al., 2014) instead of the prohibiting "no".

The third study presented in the present thesis was the first that broadly characterized individuals regularly using methylphenidate for cognitive enhancement by applying an extensive neuropsychological test battery. Previous studies addressed single personality traits and demographic characteristics of cognitive enhancement users without differentiating between those who used pharmacological cognitive enhancement on trial and those who used psychoactive substances repeatedly as study aid. The comparison with stimulant-naïve controls and, in a broader sense, also the comparison of personality features with recreational stimulant users, was progressive and may enlighten the neuroenhancement debate.

A further important strength was the urine and hair testing to verify self-report data on psychoactive substance use and to ensure that cognitive task outcomes were unbiased by substance use.

5.6 Limitations

A number of limitations need to be considered. The first and main limitation of the studies presented in this thesis is their cross-sectional design. Therefore, no causal relations can be drawn from the results and only associations could be established. Nevertheless, the use of theoretical models provides evidence about plausible relationships which could be investigated in further studies. The personality characteristics used to differentiate between pharmacological cognitive enhancement users and stimulant-naïve controls have been shown to be antecedent causes of individual differences in psychopathology and personality disorders. These limitations warrant further work on pharmacological cognitive and mood enhancement in longitudinal studies.

A second limitation of the conducted study is the use of the LINK Internet panel to estimate the prevalence of neuroenhancement in Switzerland because this leads to a double self-selection bias. The first bias might have occurred during the computer-assisted telephone recruitment interviews for the Internet panel. Even if this panel is representative for the Swiss population, not every individual will be equally willing to participate in public opinion surveys. Therefore, the prevalence of neuroenhancement in Switzerland might be underestimated if employees and students experiencing high stress would deny participation, as this is a predictor of pharmacological neuroenhancement. The second self-selection bias might have occurred as a consequence of the survey topic since we invited the panelists to participate in a survey about stress and stress management strategies at work and in education. Although it was a topic appealing to anyone who met the inclusion criteria (employed or being a student), it is possible that those affected by stress and associated problems were more likely to talk about stress and coping strategies. Contrarily, those with high stress might not have had time to respond to this large-scale survey. However, the frequency of stress in the past 12 months was slightly higher than in the stress study among Swiss employees, so this might confirm the continuously increase of perceived stress among Swiss employees over the years (Grebner et al., 2010).

Thirdly, the current research was limited by the use of self-reported data, which might be subject to perceptual bias and socially desired responses. However, we addressed this issue in all studies to minimize its influence as far as possible and informed potential respondents that participation was voluntary and all survey procedures provided full anonymity. Moreover, web-based self-administered questionnaires lead to higher reporting rates of substance use (Wang et al., 2005) and the use of a national Internet panel to assess the prevalence of nonmedical drug use has shown to be a good strategy (Novak et al., 2007). We controlled for

random answering behavior by presenting two fictitious medications and only a negligible small number of participants reported the use of those drugs. Confidence in our findings is supported by the low prevalence of self-reported pharmacological neuroenhancement and the reasonable prevalence for alcohol, nicotine, and illegal drug use which are comparable to the prevalence rates reported by the Swiss Addiction Monitoring (Gmel et al., 2013). Especially students showed a considerably openness to report nonmedical prescription drug and illegal drug use in Internet surveys and misreporting seemed to be unlikely (Maier et al., 2013; Ott & Biller-Andorno, 2014). However, the self-reported drug use of healthy cognitive enhancement users and stimulant-naïve controls in the third study were verified by urine and hair testing which was an important strength. The potential perceptual bias when answering the personality questionnaires (Cloninger & Zohar, 2011) was equal for cognitive enhancement users and not problematic in previous studies among cocaine users (Preller, Herdener, et al., 2014; Vonmoos, Hulka, Preller, Jenni, Schulz, et al., 2013)

A further limitation was the small sample size in the third study that compared only 25 healthy individuals with regular methylphenidate use for cognitive enhancement with 39 stimulant-naïve controls. Despite the possibility of contacting individuals who reported cognitive enhancement in previous studies (Maier et al., 2013; Maier & Schaub, 2014) and additional advertisement it was exceptionally difficult to find regular nonmedical methylphenidate users without both ADHD diagnosis and concurrent illegal drug use. The personal interviews with potential study participants revealed that most of them had used methylphenidate only on an experimental basis or sporadically. In combination with the low prevalence of pharmacological cognitive enhancement in the general population survey and the finding that pharmacological cognitive enhancement among students is often limited to exam preparation (Maier et al., 2013), it can be concluded that the group of healthy cognitive enhancement users is only a very small one. The recruitment of healthy individuals with regular methylphenidate use for cognitive enhancement took more than one year and, therefore, did not conflict or generally overlap with academic exam periods.

5.7 Implications

5.7.1 Implications for policy and prevention

Taken together, the findings of the present thesis do not support the often raised assumption that neuroenhancement might spread in the near future (Greely et al., 2008). Several prescription drugs are potentially effective to enhance cognition in healthy individuals but their effectiveness cannot be generalized. The same drug can have different effects in

different individuals as well as different outcomes on performance within the same individual, depending on dose, task, brain plasticity, current physical and mental condition, and personality (de Jongh et al., 2008; Wood et al., 2014). This list of factors that may influence the effectiveness of a drug off beyond its actual mechanism of action is not conclusive and shows the complexity of the debate.

Occupational health has to consider new challenges in the near future irrespective of whether or not pharmacological neuroenhancement will spread. Therefore, prevention of tobacco, alcohol, and illegal drug use at work has to be extended to include prescription drug misuse. Especially big companies with high competitive pressure should be vigilant concerning employee's psychoactive substance use to enhance performance at work. Furthermore, illicit substance use prevention for pharmacological neuroenhancement should directly or indirectly be fostered even though this behavior might maximize the economic benefit of a company in the short-term. Mohamed (2014) claimed that increased economic benefit, however, is not equal to greater well-being and happiness for society. Thus, the dialogue between management and employees to account for employee's well-being is strongly recommended.

An open dialogue might also help those individuals with current medical treatment for a mental disorder to reflect their additional self-medication and to become aware of associated risks (Ruiz, 2010). Pharmacological neuroenhancement as serious self-medication to cope with symptoms of a mental disorder and associated stress was identified as an important public health issue that has, to date, achieved minor attention. The assumption that cognitive enhancement among healthy individuals will widely spread and become a desirable means to improve work and study performance in the general public was not supported by the present findings.

Prevention of pharmacological neuroenhancement is probably more difficult to address at universities. Students know exactly which tests they have to pass and which diplomas they would like to achieve in a specific time. Due to the limited time as a student, which is only a transit to "real" employment life, it is easy to self-legitimate the use of pharmacological neuroenhancement only for one or more exam periods. The findings in the present thesis confirm that students are more willing to use prescription drugs or illegal drugs to improve their academic performance compared to employees. This might be a generation effect that will disappear in the future because similar to the normalization of recreational drug use (Sznitman et al., 2013), it might indeed become normal for a certain group of students to test pharmacological neuroenhancement during their studies. If policy considered regulations to

prevent pharmacological neuroenhancement by healthy individuals, a case-by-case regulation of drugs which are off-label-used for enhancement purposes is recommended (Dubljević, 2013). Even different regulations of the same substance based on different release forms (instant vs. extended) might be considered (Dubljević, 2013). Moreover, regulations should aim at minimizing the risks and harms of pharmacological neuroenhancement while maximizing the benefits (Ragan et al., 2013). Recently, the Swiss Federal Council has announced that there is no need for additional regulations among ADHD medications because the misuse of these drugs in Switzerland is rather low (Eckhardt, 2014).

As long as no prescription drug is developed specifically for neuroenhancement, neuroenhancement with prescription drugs will remain an off-label use. Physicians are not obliged to respond on neuroenhancement requests but they are allowed to prescribe adult patients drugs for neuroenhancement following guidelines of off-label drug prescription (Larriviere, Williams, Rizzo, & Bonnie, 2009). Swiss practitioners show a considerable openness regarding the prescription for medication for neuroenhancement as long as the level of an individual's suffering was perceived as high and no therapeutic alternatives were available (Ott et al., 2012). Practitioners are not familiar with the term neuroenhancement but they are generally willing to improve the well-being of their patients in the absence of disease as well to improve their quality of life (Ott et al., 2012; Ragan et al., 2013). Moreover, our findings revealed that physicians were the most common source of supply for drugs used for pharmacological mood enhancement. Thus, it is hypothesized that prescriptions for pharmacological mood enhancement are already common practice in Switzerland while more concerns are raised at pharmacological cognitive enhancement.

However, there are many non-pharmacological means for cognitive enhancement which have received relatively little attention in the neuroenhancement debate such as sleep, nutrition, cognitive training, or physical exercise, all of which should be promoted more strongly (Dresler et al., 2013; Maier & Schaub, 2015). It is important to address the question whether all available non-pharmacological alternatives have been fully utilized, especially for scenarios in which pharmacological neuroenhancement might seem to be the best solution (Russo, 2007).

Finally, moderate and serious self-medication and associated mental health issues first have to be acknowledged as worthy of dealing with by policy and practitioners. A campaign to objectively inform the public about prescription drug use, associated indications, and misuse potential, as suggested by Eckhardt (2014), seems to be a good preventive instrument. Objective information about potentials and risks and the diminishment of public fear and

stigma regarding prescription drugs and disorders will be an important step to take. Moreover, it is important to provide the public with essential evidence-based information about pharmacological neuroenhancement and the associated risks and safety concerns. We should not be afraid of informing about both, positive and negative implications of pharmacological neuroenhancement in healthy individuals. Consistent with other European studies, our findings indicate that the willingness to use prescription drugs or illegal drugs for neuroenhancement is rather low (Sattler et al., 2014).

5.7.2 Implications for future research

The findings of the three studies have important implications for future research and the understanding of pharmacological neuroenhancement in its different forms. Underlying motives for neuroenhancement substance use are not limited to cognitive enhancement only and warrant more detailed investigation due to their complexity. A reasonable approach to better understand consumption motives could be to investigate the causality of relationships in longitudinal studies. Therefore a welfarist approach (Earp et al., 2014) which focuses on an individual's mental health that can, but not necessarily has to be associated with improved cognitive performance, is recommended. Nevertheless, communicating recent research findings is crucial to dispel popular myths regarding pharmacological neuroenhancement (Arria & DuPont, 2010). As our study findings indicate, there is only a very specific group that might benefit from pharmacological neuroenhancement, while the expectations of the drug's effect are often not met. Hence, further studies should address the point prevalence of pharmacological neuroenhancement more strongly to avoid reporting a high lifetime prevalence that is likely to be based on several curious experimental users.

Monitoring the development of pharmacological neuroenhancement in Switzerland is essential in order to develop effective policy responses. Nevertheless, future research should transfer from first-world problems with self-optimization of already good functioning to the preservation and recovery of health of vulnerable groups in the public. Moreover, while regular prescription drug misuse for cognitive and mood enhancement in Switzerland is rare, regular use of alcohol and cannabis to relieve stress or to improve academic performance is more common and affects physical and mental health. Future research on pharmacological neuroenhancement considering the complexity of psychoactive substance use for improved performance at work and in education is therefore recommended. Building on the present findings, future studies should not be limited to healthy individuals and use longitudinal designs.

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